SAGA PROTOCOL COVER PAGE

Official Title	A Phase 2/3 Multicenter, Randomized, Double-masked, Parallel-group, Placebo-controlled Study to Investigate the Safety, Pharmacokinetics, Tolerability, and Efficacy of ALK-001 in Geographic Atrophy Secondary to Age-related Macular Degeneration
NCT Number	NCT03845582
Document Date	01-Feb-2019

CLINICAL TRIAL PROTOCOL

Official Title	A Phase 2/3 Multicenter, Randomized, Double-masked, Parallel-group, Placebo-controlled Study to Investigate the Safety, Pharmacokinetics, Tolerability, and Efficacy of ALK-001 in Geographic Atrophy Secondary to Age-related Macular Degeneration
Brief Title	Phase 2/3 Study of ALK-001 in Geographic Atrophy (SAGA)
Sponsor	Alkeus Pharmaceuticals, Inc. 278 Elm St, Suite 229 Somerville, MA 02144 Direct Cell: +1.617.412.0644
Study Drug	ALK-001 (C20-D3-Retinyl Acetate, C20-D3-Vitamin A Acetate)
IND	108,353
Protocol Number	ALK001-P3001 (NCT Registration: TBD)
Monitor	[redacted]
Compliance	This study will be conducted in accordance with standards of Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and all applicable federal and local regulations
Version:	v1.0

Previous revisions: **N/A**

Contents:

List of Abbreviations

ABCA4: ATP Binding Cassette Sub family A Member 4
A2E: N-retinylidene-N-retinylethanolamine (a representative RDDB)
AE: Adverse Event
ALK-001: C20-D3-retinyl acetate. The investigational drug assessed in this study.
ANOVA: Analysis of Variance
ALT: Alanine Aminotransferase
AMD: Age-related Macular Degeneration
AP: Alkaline Phosphatase
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
ATR: All-trans-retinal
BCVA: Best Corrected Visual Acuity
bHCG: Human Chorionic Gonadotropin
CBC: Complete Blood Count
CNV: Choroidal Neovascularization
CS: Clinically significant
CSR: Clinical Study Report
CRF: Case Report Form
ECG: Electrocardiogram
ERG: Electroretinogram
ETDRS: Early Treatment Diabetic Retinopathy Study
EVA: Electronic Visual Acuity
FAF: Fundus Autofluorescence
FDA: Food and Drug Administration
GA: Geographic Atrophy
GCP: Good Clinical Practice
HIPAA: Health Insurance Portability and Accountability Act
IND: Investigational New Drug
IOP: Intraocular Pressure
IRB: Institutional Review Board
IReST: International Reading Speed Texts
MP: Microperimetry
NCS: Non Clinically Significant
OCTA: OCT Angiography
PHI: Protected Health Information
PK: Pharmacokinetics
PRO: Patient Reported Outcome
RBP: Retinol Binding Protein
RDDB: Retinaldehyde Derived Dimerization Byproducts
RPD: Reticular Pseudodrusen
RPE: Retinal Pigment Epithelium
SAE: Serious Adverse Event
SD-OCT: Spectral Domain Optical Coherence Tomography
SMC: Safety Monitoring Committee
SOP: Standard Operating Procedures
ULN: Upper limit of normal
VF-14: Standardized visual function test with 14 questions

1.1 STUDY SYNOPSIS

Official Title	A Phase 2/3 Multicenter, Randomized, Double-masked, Parallel-group, Placebo-controlled Study to Investigate the Safety, Pharmacokinetics, Tolerability, and Efficacy of ALK-001 in Geographic Atrophy Secondary to Age-related Macular Degeneration
Brief Title (Acronym)	Phase 2/3 Study of ALK-001 in Geographic Atrophy ("SAGA")
Protocol Number	TBD
Version	v1.0
Phase	Phase 2/3
Methodology	This is a multicenter, randomized, double-masked, parallel-group, placebo-controlled study to assess the safety and efficacy of orally-administered ALK-001 (C20-D3-retinyl acetate) in subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Subjects, 60 years of age or older, who have been diagnosed with GA consecutive to AMD, and who have no evidence of other conditions that might confound the diagnosis, progression, and measurement of GA lesions, will be invited to participate. Subjects must be deemed sufficiently healthy and likely to complete the full two-year duration of the study. For these subjects: - **at least one eye** (the "**study eye**") must have GA with (**i**) no concurrent or history of choroidal neovascularization (CNV), (**ii**) total GA lesions adding up to a total area between approximately 1.5 sqmm and 20 sqmm, (**iii**) in the case of multifocal GA lesions, at least one contiguous GA lesion measuring approximately 1 sqmm or more, (**iv**) edges of GA lesions presenting with hyperautofluorescent patterns, and (**v**) an early treatment diabetic retinopathy study (ETDRS) best-corrected visual acuity (BCVA) of 33 letters or more (approx. 20/200). In case of foveal sparing, the shortest distance of GA borders to the fovea must be under approximately 250 µm. - the "**fellow eye**" (also called non-study eye), must present with one of the following: (**a**) reticular pseudodrusen (RPD), (**b**) intermediate AMD with at least one macular drusen greater than approximately 125 µm in diameter, (**c**) active or history of CNV, (**d**) geographic atrophy due to age-related macular degeneration, with or without a history of, or concurrent CNV. This study will enroll up to approximately n = 300 subjects. At the start of the screening period, subjects will be given a supply of placebo capsules to measure their compliance during a screening period lasting 20 to 40 days. Subjects who match all eligibility criteria and are deemed adequately compliant during the screening period, will be randomized to receive the study drug ALK-001 (n = 200) or placebo (n = 100) for a treatment period of 2 years. Following the initial treatment period, subjects will have the option to continue treatment in an optional open-label extension period (which will be fully described in future protocol amendments). Subjects who have participated in previous clinical trials may only be eligible upon approval by sponsor, which may be granted if the subject has documented evidence to have received the placebo/sham during such previous trials. Study participants, clinical team and sponsor staff in charge of day-to-day activities will be masked to the treatment group throughout the study. A Safety Monitoring Committee (SMC) will periodically review the safety data. A Statistical Analysis Plan (SAP) will detail analyses to be performed by independent statisticians.
Sample Size	With 300 subjects enrolled in the study and assuming that 80% of subjects are evaluable for the primary outcome measure, the study has an **80% power to detect, after 24 months of treatment, a 33% slowing in GA growth rate with a 2-tailed significance of 0.05** (assuming a standard deviation of 1.5 sqmm/year and an average progression of 1.8 sqmm/year in the control group)**.** As an exploratory measure and assuming that 35% of enrolled subjects have a fellow eye with active or history of CNV, the study has an **80% power to detect, after 24 months, a 75% reduction in incidental progression to CNV in the study eye** with a 1-tailed significance of 0.2 (Fisher's exact test).

Scientific Rationale	GA is an advanced form of AMD, characterized by well-demarcated atrophic lesions of the RPE and outer retinal layers. Symptoms of GA include uncorrectable central vision loss and other disturbances, along with the inability to see fine details, read, write, recognize faces, or drive. GA is currently untreatable, progressive, and leads to legal blindness. Retinaldehyde-derived dimerization byproducts (RDDB) are molecules that form non-enzymatically in the retina as byproducts of the visual cycle. RDDBs include molecules such as "A2E" and other vitamin A dimers, as well as their downstream degradation or combination byproducts. RDDBs form and gradually accumulate with age in the retina. These molecules are toxic to the retina and have been shown to cause chronic oxidative stress, inflammation, dysregulation of the complement, angiogenesis, poisoning of the lysosomes, etc., which are thought to contribute to the pathophysiology of AMD. Strategies to prevent RDDB formation have been explored as possible treatments of GA. To date, these strategies have relied on "modulating the visual cycle", by decreasing the vitamin A supply or its flow in the retina. Such approaches lead to adverse reactions such as night blindness, dark adaptation delays and chromatopsia, and might lead to long-term retinal toxicity. ALK-001 is a chemically-modified vitamin A whereby 3 hydrogen atoms have been selectively replaced by heavy hydrogen (also known as "deuterium"). Because deuterium and hydrogen are similar, ALK-001 preserves normal biological functions of vitamin A. Daily intake of ALK-001 leads to rapid replacement of the majority of vitamin A with one that forms RDDB several folds slower, without affecting the visual cycle. As such, ALK-001 is not a visual cycle modulator. ALK-001 is a "clean tool" that can be used in clinical studies to measure the extent to which slowing RDDB formation retards the progression of GA and the incidence of CNV.
Study Duration	Approximately 3 years, including 8 months of enrollment, 24 months of treatment period, and 4 months of data analysis.
Study Center(s)	Multicenter.
Primary Objective	To assess the effects of ALK-001 on the growth rate of GA lesions after 24 months of treatment in patients with GA associated with AMD.
Secondary Objectives	• To assess the safety and tolerability of ALK-001 in patients over 60 • To assess the pharmacokinetics of ALK-001 in patients over 60 • To assess the effects of ALK-001 on the growth of GA lesions after 12 months of treatment • To assess the effects of ALK-001 on the growth of GA lesions between 6 and 24 months of treatment • To assess the effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has CNV • To assess the effects of ALK-001 on visual function, including BCVA, LLVA, reading speed, questionnaires on quality of life and vision
Exploratory Objectives	• To assess the effects of ALK-001 on retinal anatomy (photoreceptors as measured by SD-OCT) • To assess the effects of ALK-001 on retinal function (measured by microperimetry) • Effects of ALK-001 on drusen characteristics • Effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has intermediate AMD • Effects of ALK-001 on the incidence of advanced AMD (CNV or GA), when the fellow eye has intermediate AMD • Distance of Preferred Retinal Locus (PRL) to foveal center and other fixation characteristics • Association between ALK-001 treatment effects and genetics • Association between ALK-001 treatment effects and complement
Number of Subjects	300 subjects, 60 years and older at the time of screening or randomization
Study Product, Dose, Route, Regimen	one capsule, containing ALK-001 or placebo, self-administered, once a day

Allocation of Subjects per Treatment Group	• ALK-001 (n = 200) • Placebo (n = 100)
Diagnostic code (ICD-10 classification)	Unilateral or bilateral advanced atrophic AMD with (**H35.31X4**) or without (**H35.31X3**) foveal involvement, consecutive to non-exudative (dry) AMD (**H35.31X0**), where X = 1 (right eye) or X = 2 (left eye) *For the study eye:* *H35.3113 Nonexudative age-related macular degeneration, right eye, advanced atrophic without subfoveal involvement* *H35.3114 Nonexudative age-related macular degeneration, right eye, advanced atrophic with subfoveal involvement* *H35.3123 Nonexudative age-related macular degeneration, left eye, advanced atrophic without subfoveal involvement* *H35.3124 Nonexudative age-related macular degeneration, left eye, advanced atrophic with subfoveal involvement* *H35.3133 Nonexudative age-related macular degeneration, bilateral, advanced atrophic without subfoveal involvement* *H35.3134 Nonexudative age-related macular degeneration, bilateral, advanced atrophic with subfoveal involvement* *H35.3193 Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic without subfoveal involvement* *H35.3194 Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic with subfoveal involvement*
Reference Therapy	Placebo
DMC	An independent SMC will perform ongoing data reviews according to a SMC charter.
NCT Registration Number	TBD
Visit Schedules	Visit schedules will follow standard of care practices: study visits will take place every 6 months to check for AEs, compliance, clinical labs, and perform ocular testing and imaging. Short optional safety-only visits can take place every 3 months. See Events table in Section 1.2 for details.
Efficacy Outcome Measures	GA lesions as measured on FAF images and verified by SD-OCT, incidence of CNV by fluorescein angiography or OCT-angiography, retinal anatomy by SD-OCT, visual function questionnaires, qualify of life questionnaire, reading speed, ETDRS BCVA, low luminance BCVA, retinal sensitivity by fundus-tracking microperimetry (optional).
Safety Outcome Measures	Adverse events (AEs), serious AEs, clinical laboratory (biochemistry, hematology, lipids, glucose, vitamin A), physical exam, ocular exam, 12-lead ECG, vital signs, vision questionnaires.
Pharmacokinetic Parameters	Plasma vitamin A and ALK-001 metabolites
Statistical Methodology	*A detailed statistical analysis plan will be prepared prior to any efficacy unmasked data analysis.* • Safety and tolerability will be summarized with descriptive statistics and individual patient narrative when necessary (SAEs, drop-out for safety, etc). • Pharmacokinetics will be analyzed with descriptive statistics. Percentage of deuterated vitamin A in plasma will be computed. • Efficacy will be assessed by comparing the following variables in subjects receiving ALK-001 vs. placebo: growth rate of GA lesions in the study eye, incidence of CNV in the study eye, changes in BCVA, changes in reading speed, changes in retinal sensitivity.

Inclusion Criteria	**All the following inclusion criteria must apply at screening, <u>except upon sponsor's approval</u>.** *<u>General</u> inclusion criteria:* 1. Male or female 60 years and older. 2. Healthy as judged by investigator. 3. Has signed and dated the informed consent form. 4. Is able and willing to perform the study procedures. 5. Is able and willing to comply with the schedule of the study visits. 6. Is able and willing to self-administer the study drug. 7. Is able and willing to follow the instructions and comply with the avoidance of vitamin A supplements. 8. Is likely to complete the 2-year study as judged by the investigator. *At least one eye, designated as the "<u>study eye</u>", must meet all the following inclusion criteria:* 9. Study eye displays well-demarcated GA lesion(s) measuring a total area between approximately 1.5 sqmm and 20 sqmm, measured on fundus autofluorescence imaging (FAF), as confirmed by sponsor or designee. 10. Study eye presents hyperautofluorescent borders in the junctional zone of GA, as confirmed by sponsor or designee. 11. If GA lesions are multifocal in the study eye, one lesion at least must be approximately 1.00 sqmm or greater. 12. In case of foveal sparing, the smallest distance between GA border and foveal center must be under approx. 250 µm. 13. All GA lesions in the study eye must fit entirely within the 30-degree retinal imaging field centered on fovea. 14. Study eye has ETDRS BCVA of 33 letters (~20/200) or better. 15. Study eye has clear or adequate ocular media and pupillary dilation, including no allergy to dilating eyedrops, to permit good quality retinal imaging as judged by the investigator. *The non-study eye, designated as the "<u>fellow eye</u>", must meet all of the following inclusion criteria:* 16. Fellow eye presents with one of the following features: (**a**) reticular pseudodrusen (RPD), (**b**) intermediate AMD with at least one macular drusen greater than approximately 125 µm in diameter, (**c**) active or history of CNV, (**d**) geographic atrophy with or without a history of, or concurrent CNV.
Exclusion Criteria	**All the following exclusion criteria must <u>not</u> apply, <u>except upon sponsor's approval</u>.** *<u>General</u> exclusion criteria:* 17. Active or historical medical condition (systemic or ophthalmic), which in the opinion of the investigator, may prevent performance of study procedures, compliance with the protocol, or continuous participation of the subject throughout the 2-year duration of study. 18. Currently taking or has taken medications associated with retinal toxicity, except for short durations as judged by investigator. 19. Is currently taking oral retinoids or medications that might affect absorption, metabolism, or function of vitamin A. 20. Has participated in any drug or device trial within 60 days of randomization. 21. Anticipates participating in any other drug or device trial over the next 2 years. 22. Is hypersensitive or allergic to fluorescein. 23. Has clinically-significant abnormal laboratory result(s) at screening, which in the opinion of the investigator, makes the patient unsuitable for study participation. 24. Has clinically-significant abnormal physical exam finding(s) at screening, which in the opinion of the investigator, makes the patient unsuitable for study participation. 25. Has active or historical, acute or chronic, liver disorder except when benign. 26. Has a clinically-significant cardiac abnormality, a clinically-significant abnormal ECG, or a marked prolongation of QTc at screening (>460 msec for male or >480 msec for female, approximately). 27. Female of childbearing potential, pregnant, lactating or positive serum pregnancy test at screening. *<u>Study eye</u> exclusion criteria:* 28. Study eye has historical or active CNV. 29. Study eye has myopia of -6 diopters or more approximately, except if retinal imaging can be properly focused. 30. Study eye has GA thought or proven to be caused by any condition other than AMD. 31. Study eye has GA lesions expected to (i) expand larger than the imaging field of view, or (ii) merge with other retinal features (optic disc or peripapillary atrophy, other non-AMD atrophic lesions, etc.) during the 2 years of the study. 32. Subject, in the case of a systemic treatment, or study eye, in the case of a monoocular treatment, has previously received treatment, surgery or procedure for GA or AMD, including clinical trials, except when there is documented evidence that the subject was receiving placebo or was part of a sham group. 33. Study eye has active or history of ocular disorder, which may confound assessment of the retina morphologically or functionally, as judged by investigator. 34. Study eye has active or history of glaucoma, uncontrolled elevated intraocular pressure, retinal detachment, RPE tear, recurring uveitis, retinal vein occlusion, diabetic retinopathy, diabetic macular edema. 35. Study eye has history of submacular or intraocular surgery, vitrectomy, or device implantation (except IOL). 36. Study eye has received intravitreal injections or cataract surgery within 90 days of randomization. 37. Study eye is expected to require cataract, epiretinal membrane, or ocular surgery over the next 2 years as judged by investigator.

Study Procedures and Assessments	The Events table in Section 1.2 displays the timing of events and all evaluations for the study. See protocol for details on each evaluation as well as the specific order of procedures to follow, if any. The following lists all study evaluations: - Informed consent - Demographics - Medical history - Choice of study eye - Comprehensive (baseline) or simplified (follow-ups) physical exam or assessment - Prior and concomitant medications - Vital signs - 12-lead electrocardiogram (ECG) - Eye exam - ETDRS Best-Corrected Visual Acuity (BCVA) - Low luminance visual acuity (LLVA) - Reading speed (MNREAD and International Reading Speed Test IReST) - Color fundus photograph (CFP) - Fluorescein Angiogram (FA) or OCT angiography (OCTA) - Fundus Autofluorescence (FAF) - Spectral Domain Optical Coherence Tomography (SD-OCT) - Microperimetry (where available) - Blood draw for clinical laboratory testing: Biochemistry, Hematology, Lipids, Pharmacokinetics - Blood draw for complement analysis and genotyping - Pregnancy test (serum) - Treatment emergent adverse events (TEAE) and serious adverse events (SAE) - Information on vitamin A & quiz - Questionnaires: Visual Function 14 (VF-14), Functional Reading Independence (FRI), Macular Disease Dependent Quality of Life (MacDQOL) - Verification of eligibility (inclusion/exclusion) - Randomization and drug dispensing - Monthly check-up phone calls - Compliance and study drug reconciliation

FAQ:

1. In general what kind of patients are you looking for?

Patients 60 years old and above, with unilateral or bilateral GA. At least one eye must have pure GA (no history or concurrent CNV) and total GA lesions between 1.5 and 20 sqmm. The fellow eye can have either pure GA, concurrent or a history of CNV, CNV and concurrent GA, or intermediate AMD with at one large macular drusen, or reticular pseudodrusen.

Patients should be deemed sufficiently healthy to complete the 24-month duration of the study. Comprehensive visits will be every 6 months with short optional safety visits every 3 months.

2. Can patients who previously entered clinical trials participate?

Yes, but only if such patient has documented evidence that they received the placebo.

3. What other non-AMD conditions or drugs can cause atrophic patches?

Several retinal diseases and dystrophies, systemic conditions, and drug-induced toxicity can cause atrophic patches that can be confused with AMD. Examples include Stargardt disease, pattern dystrophy, RPE tears,

trauma, hemorrhage, drug-induced toxicity (hydroxychloroquine, didanosine, thioridazine, etc.), choroidal sclerosis, Bietti's crystalline dystrophy, etc.

Subjects thought to have GA consecutive to any other condition than AMD will not be enrolled.

4. Can subjects take AREDS2 supplements during the study?

Yes, AREDS2 will be allowed and recommended for all patients, especially those with intermediate AMD in the fellow eye.

5. Can subjects take other "eye" supplements during the study?

No, except upon exception by sponsor.

6. Can subjects take vitamin A-containing supplements or foods containing vitamin A or beta-carotene?

Subjects should simply avoid vitamin A or beta-carotene containing supplements, as well as food products containing overly high amounts of vitamin A such as liver or liver-based products/oils, giblets or other animal's internal organs, highly concentrated/processed fruit juices. All fruits and vegetables in their "natural", unprocessed form/concentration, are acceptable without restriction.

7. What happens to patients who develop CNV in the study eye? In the fellow eye?

Patients who develop CNV in the study eye continue the study and receive standard of care treatment as determined by each PI.

8. Can patients with history of or active CNV enroll?

Yes, as long as at least one eye has "pure GA" with no history or active CNV.

9. Are subjects stratified?

No.

10. What are the expected outcomes for each eye based on their respective baseline?

Study Eye	Fellow Eye	Primary outcome	Secondary outcome
Pure GA	CNV	GA growth rate in study eye	Incidence of CNV in study eye (natural hx reports approx. 20% incidence at 24 months)
Pure GA	GA with or without CNV	GA growth rate in study eye	GA growth rate in fellow eye; Incidence of CNV in study eye (natural hx report approx. 3-6% at 24 months)
Pure GA	Intermediate AMD with RPD or large macular drusen	GA growth rate in study eye	Incidence of advanced AMD (CNV or GA) in fellow eye (natural hx reports approx. ~20% incidence at 24 months)

1.2 EVENTS TABLE (INITIAL PERIOD)

Period		Screening/Baseline and Run-In[15] Period		Initial Treatment Period																
Study Months (m)		between approx. 20 and 40 days before day 1	Day 1 Start of Treatment	Day 2-3 mo	3 mo	3-6 mo	6 mo	6-9 mo	9 mo	9-12 mo	12 mo	12-15 mo	15 mo	15-18 mo	18 mo	18-21 mo	21 mo	21-24 mo	24 mo End of Study	Early Termination[13]
Visit Window				monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	
Visit (V) #	Standard of Care CPT Code	V01 Screening start Run-in[15] period starts	V02 Screening end/ Baseline/ Randomization	Phone Follow-up	V03	Phone Follow-up	V04	Phone Follow-up	V05[12] (Optional)	Phone Follow-up	V06	Phone Follow-up	V07[12] (Optional)	Phone Follow-up	V08	Phone Follow-up	V09[12] (Optional)	Phone Follow-up	V10	ET (Early Termination)
Screening Period																				
Informed Consent	-	●																		
Size 0 Capsule Swallow Test	-	O																		
Demographics	-	●																		
Clinical Diagnosis	-	●																		
Medical, Surgical, and Ocular History	-	●																		
Collection of Historical Retinal Images	-	●																		
Vitamin A information, counseling & quiz[8]	-	●																		
Eligibility (Inclusion/Exclusion) Criteria	-	●	●																	
General Health																				
Prior and concomitant medications	-	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Treatment Emergent Adverse Events (AE) and SAEs	-			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Check-up phone calls	-			●		●		●		●		●		●		●		●		
Study Drug Reconciliation	-				●		●		O[12]		●		O[12]		●		O[12]		●	●
Vital signs	-	●	●		●		●		O[12]		●		O[12]		●		O[12]		●	●
12-Lead ECG	93005	●									●								●	O[13]
Physical Exam or Assessment[1]	99396	C					ACI / RC				● RC				ACI / RC				● RC	O[13]
Eye Exam[2]	92014	●					ACI / RC				● RC				ACI / RC				● RC	O[13]
Quality of Life and Visual Function																				
Visual Acuity (ETDRS-BCVA)[2]	92015	●	●				●				●				●				●	O[13]
Low Luminance Visual Acuity (LLVA)[2]	99173	●	●				●				●				●				●	O[13]
Reading Speed (IReST, MNREAD)[2]	-	●	●				●				●				●				●	O[13]
Vision Questionnaires (VF14, FRI)	-	●					●				●				●				●	O[13]
Ocular Imaging																				
Color Fundus Photograph (CFP)[2]	92250	●					ACI / RC				● RC				ACI / RC				● RC	O[13]
OCT Angiography (OCTA) or Fluorescein Angiogram (FA)[2]	92134 or 92235	●					● RC				● RC				● RC				● RC	ACI/RC
Fundus Autofluorescence (FAF)[2]	92250	●	● if screening older than 1 mo.				● RC				● RC				● RC				● RC	O[13]
Spectral Domain OCT (SD-OCT)[2]	92134	●					● RC				● RC				● RC				● RC	O[13]
Treatment																				
Treatment of CNV[16]	67028	ACI / RC	ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC	ACI / RC
Psychophysical function																				
Microperimetry[2]	92083	●	●				● RC				● RC				● RC				● RC	O[13]
Clinical Laboratory (Central Lab)																				
Biochemistry[3]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Hematology[4]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Lipids[5]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Glucose[14]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Vitamin A and Pharmacokinetics (PK)[6]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Complement[17]	-	See footnotes																	O	O[13]
Genotype[17]	-	See footnotes																		
Pregnancy Test[7]	-	O																		
Miscellaneous																				
Randomization	-		●																	
Drug Dispensing[9]	-	● Placebo	●		●		●		●		●		●		●		●			

● : Protocol Procedure O : Optional ACI/RC: Perform As Clinically Indicated or for Routine Care

1 Comprehensive physical exam (C) or simplified physical exam (S) when performed by PI or delegated personnel; Limited physical assessments when performed off-site by a home nurse.
2 Both eyes.
3 Biochemistry (CMP panel, fasting): Sodium, Potassium, Chloride, Bicarbonate, Urea, Creatinine, Calcium, Total Protein, Bilirubin, Albumin, Alkaline phosphatase, AST, ALT
4 Hematology (differential, fasting): WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBC, HGB, HCT, MCV, MCH, PLT
5 Lipids (fasting): total cholesterol, triglycerides, HDL, LDL
6 Collect approx. 6 mL of blood, extract plasma (~ 2 x 1.5 mL), store at below -20°C in provided glass vials, ship in bulk upon request by sponsor.
7 Optional. As determined by the PI.
8 Self-administered short quiz to ensure subject understands the instructions
9 Investigator may dispense the appropriate number of bottles until the next visit (usually 3 or 6 bottles). At screening, a bottle containing placebo is dispensed to check subject's proper compliance at V02. Check numeral 15.
10 This final, exit visit shall occur 3 months after permanent discontinuation of the study drug or completion of the treatment period
11 Reasonable exceptions may be granted by sponsor if such exception would not be expected to influence data collection or continuous treatment of the study subject
12 Optional procedures performed if visit is done in person. Upon investigator's decision and if the subject does not have ongoing adverse events that are possibly associated with the study drug, this visit can be replaced by a phone call. Study drug is then directly shipped to the subject and in person assessments are not performed.
13 Perform optional procedures only if the early termination visit occurs at least 3 months following one of the major visits (in grey background): V04, V06, V08 and V10. Ask sponsor if unsure.
14 Glucose (fasting): HbA1C
15 Run-In period: all screen subjects may start receiving placebo for approximately 4 weeks to measure compliance. Only those subjects with greater than 80% adherence during the run-in period will be randomized
16 Proceed according to the PI's standard of care.
17 Genotype and complement can be measured at any time during the study upon sponsor's request. This will be done through central labs.

1.3 EVENTS TABLE (OPTIONAL, OPEN LABEL EXTENSION PERIOD)

Period	Extension Period							
Study Months (m)	24-30 mo	30 mo	30-36 mo	36 mo	36-42 mo	42 mo	42-48 mo	48 mo end of study
Visit Window	bimonthly	±5 days[11]	bimonthly	±5 days[11]	bimonthly	±5 days[11]	bimonthly	±5 days[11]
Visit (V) #	Phone Follow-up	V11	Phone Follow-up	V12	Phone Follow-up	V13	Phone Follow-up	V14
Screening Period								
Informed Consent								
Demographics								
Clinical Diagnosis								
Medical, Surgical, and Ocular History								
Collection of Historical Retinal Images								
Vitamin A information, counseling & quiz[8]								
Eligibility (Inclusion/Exclusion) Criteria								
General Health								
Prior and concomitant medications	●	●	●	●	●	●	●	●
Treatment Emergent Adverse Events (AE) and SAEs	●	●	●	●	●	●	●	●
Check-up phone calls	●		●		●		●	
Study Drug Reconciliation		●		●		●		●
Vital signs		●		●		●		●
12-Lead ECG								●
Physical Exam or Assessment[1]		ACI / RC		ACI / RC		ACI / RC		● RC
Eye Exam[2]		SOC		SOC		SOC		● RC
Quality of Life and Visual Function								
Visual Acuity (ETDRS-BCVA)[2]		●		●		●		●
Low Luminance Visual Acuity (LLVA)[2]		●		●		●		●
Reading Speed (IReST, MNREAD)[2]		●		●		●		●
Vision Questionnaires (VF14, FRI)		●		●		●		●
Ocular Imaging								
Color Fundus Photograph (CFP)[2]		SOC		SOC		SOC		SOC
OCT Angiography (OCTA) or Fluorescein Angiogram (FA)[2]		SOC		SOC		SOC		SOC
Fundus Autofluorescence (FAF)[2]		SOC		SOC		SOC		SOC
Spectral Domain OCT (SD-OCT)[2]		SOC		SOC		SOC		SOC
Treatment								
Treatment of CNV[16]		SOC		SOC		SOC		SOC
Psychophysical function								
Microperimetry[2]		● RC		● RC		● RC		● RC
Clinical Laboratory (Central Lab)								
Biochemistry[3]		●		●		●		●
Hematology[4]		●		●		●		●
Lipids[5]		●		●		●		●
Glucose[14]		●		●		●		●
Vitamin A and Pharmacokinetics (PK)[6]		●		●		●		●
Complement				O				O
Genotype								
Pregnancy Test[7]								
Miscellaneous								
Randomization								
Drug Dispensing[9]		●		●		●		

● : Protocol Procedure O : Optional ACI/RC: As Clinically Indicated or Routine Care

1.4 PROTOCOL AMENDMENTS

Section reserved for future amendments.

1.5 BACKGROUND INFORMATION

This document is the protocol for a multi-center phase 2/3 clinical trial to evaluate the effects of ALK-001, an investigational new drug (IND), on the progression of geographic atrophy (GA) consecutive to age-related macular degeneration (AMD).

Subjects enrolled in the study will be instructed to take one capsule per day containing ALK-001 or placebo for a period of 24 months. At the end of this treatment period, subjects may be offered to enroll into an optional open-label, long-term extension, to evaluate the long-term effects of ALK-001. Up to n = 300 subjects will be enrolled in the study. Subjects will be randomized 2:1 ALK-001:Placebo without stratification.

Subjects enrolled in the study will adhere for the most part to standard of care follow-up schedule, with visits every 6 months and optional visits every 3 months. Every 6 months, subjects will perform imaging, visual function tests, and will undergo safety testing (including evaluation of adverse events, clinical lab tests, physical and/or ocular assessments). At the optional 3-month visits, subjects will perform clinical lab tests.

To cover a clinically-representative population of patients with GA, only one (1) eye will be required to have GA ("study eye"). The fellow eye is allowed to have either (**a**) GA, (**b**) intermediate AMD, characterized by a large macular drusen, or (**c**) history or active choroidal neovascularization (CNV).

The area of GA will be measured using fundus autofluorescence (FAF) imaging, characterized by well-demarcated dark lesions, confirmed on optical coherence tomography (OCT) imaging.

This study will be conducted according to US and international standards of Good Clinical Practice (GCP), applicable government regulations and institutional research policies and procedures. The sponsor of the study, Alkeus Pharmaceuticals, is dedicated to the subjects' rights and wellbeing and, prior to and during the course of the study, will ensure proper communication with and training of the investigators and clinical staff, as well as monitoring of the study. An independent Safety Monitoring Committee (SMC) will monitor safety data throughout the trial.

1.5.1 Definitions: Investigator; PI; Sponsor

In this document, the "investigator" or "study staff" will designate the principal investigator (PI), sub-investigator, as well as the clinical research team (research coordinators, ophthalmic technicians, etc.).

"PI" shall designate the PI or sub-I. The PI shall be in charge of the overall conduct of the clinical trial at his/her institution, including the delegation of protocol-related activities to properly trained personnel.

"Sponsor" shall designate the study sponsor, Alkeus Pharmaceuticals, and its affiliates or other representatives (including for example contract research organizations or other organizations acting on behalf of the sponsor).

1.5.2 PI-only procedures/assessments

Whenever the protocol specifies that the "PI" shall perform a procedure or assessment, this is to indicate that such procedure or assessment should only be performed by the PI, sub-I, or personnel with a medical license allowing them to perform such task or procedure.

"PI-only procedures" include for example: final determination of inclusion/exclusion criteria, physical exam, eye exam, treatment of CNV, ECG reading, assessment of clinical significance of clinical lab values, assessment of AE association with study drug.

1.5.3 Resolution of protocol inconsistencies

In case a section of the protocol conflicts with another section resulting in a protocol inconsistency, investigator shall request clarifying instructions from the sponsor, which shall be documented.

1.5.4 Background, Scientific Rationale and Proposed Trial

1.5.4.1 Background

The macula is located at the back of the eye in the center of the retina. When millions of cells in this light-sensitive, multilayer tissue deteriorate, central vision is lost along with the ability to read, write, drive and see colors. This so-called "macular degeneration" principally affects the elderly in a group of diseases called age-related macular degeneration (AMD). It is estimated that 8 million Americans are at risk for developing AMD.

In the United States, the prevalence of intermediate + advanced AMD increases with age from 7% (65-69 years old) to 24% (>80 years old) [1, 2]. While a treatment exists to prevent further progression of the wet form of AMD, called choroidal neovascularization (CNV), no treatment exists for over 80% of the patients with AMD or the millions at risk of developing AMD.

The long-term goal of this work is to develop an oral drug to prevent the development and slow the progression of AMD. The central hypothesis is that slowing vitamin A dimerization, an early event in the pathology of AMD, will slow the development and/or progression of the disease. In this protocol, we propose to evaluate the extent to which slowing the formation of toxic vitamin A dimers slows the progression of GA associated with AMD.

1.5.4.2 Scientific Rationale

AMD is characterized by an age-related degeneration of the retina. The root cause for this degeneration or why some people develop AMD while others do not, is unknown. Over 20 years ago, it was hypothesized that the dimerization of vitamin A may be a significant contributor to the etiology of AMD. The eye indeed uses vitamin A as a cofactor to sense light, and a striking chemical signature of the aging and degenerating retina, is the accumulation of vitamin A dimers in the retinal pigment epithelium (RPE) [3, 4] and the underlying Bruch's membrane [5]. In rodent models, high levels of vitamin A dimers correlate with poor retinal health [6-10], and a variety of mechanisms have been proposed by which vitamin A dimers may induce retinal toxicity [5, 11-

50]. For example, the vitamin A dimer A2E has been shown to solubilize lipid membranes, inactivate lysosomes by increasing lysosomal pH, and accumulate in the negatively charged mitochondrial compartment causing mitochondrial toxicity. Once dimerized, the special orientation of the polyene chains makes dimers especially susceptible to oxidative degradation [33] leading to the generation of reactive aldehydes and epoxides that can go on to crosslink biomolecules [15, 51, 52]. Dimers of vitamin A have been shown to up-regulate or directly bind to proteins involved in retinal function such as RPE65 [19], retinoic acid receptors [26], and cyclooxygenase-2 [32]. All of these mechanisms have been argued to participate in the development and progression of AMD.

Chronic activation of complement is thought to be paramount in the development and progression of AMD [53-56]. The exact triggers of complement activation are not known. Using *in vitro* and animal models, several groups have shown that dimers of vitamin A, such as A2E, directly activate complement [20, 30]. In addition, vitamin A dimers have been shown to be pro-angiogenic [23]. This suggests that the continuous formation of vitamin A dimers may directly provide an environment for chronic activation of complement and generation of vascular endothelial growth factor (VEGF) in the retina.

We have shown that long-term administration of ALK-001 to mouse models of retinal degeneration and in wild-type mice normalizes complement [57]. ALK-001 thus provides a powerful tool to chronically suppress the dimerization of vitamin A and examine the extent to which vitamin A dimers contribute to chronic activation of complement and to the development and progression of AMD.

In addition to AMD, dimers of vitamin A are found in other forms of retinal degenerations: for example genetic dystrophies known as Stargardt disease, vitelliform (or Best) macular degeneration (VMD), Sorsby's fundus dystrophy, malattia leventinese (Doyne honeycomb), and *ABCA4*-related cone-rod dystrophies all present with abnormal pigmentary changes in the retina indicative of vitamin A dimers [58-63]. These pigmentary changes, in almost all of the above conditions, precede vision loss. Based on the above observations, researchers have been feverishly developing strategies to reduce the formation of vitamin A dimers in hopes of preventing vision loss due to AMD and retinal dystrophies marked by the formation of vitamin A dimers.

Specifically, the fact that animals given vitamin A poor diets [64, 65], that animals [66] and humans [67] with genetic defects in proteins involved in the use or the delivery of vitamin A to the photoreceptors (e.g. RPE65, LRAT, RBP4) show little accumulation of these toxic vitamin A dimers, have led to the development of strategies to prevent the dimerization of vitamin A by partially depriving the photoreceptors of vitamin A. Photoreceptor deprivation is attempted by blocking the delivery of vitamin A to the eye or by inhibiting the vitamin A cycle. However, vitamin A stabilizes photoreceptor proteins, and when photoreceptors do not “contain” vitamin A, the retina undergoes degeneration. Indeed, many of the above conditions, where vitamin A delivery to the photoreceptors is impeded, such as retinitis pigmentosa, Leber congenital amaurosis, or hereditary defects in RBP4, lead to retinal degeneration. Thus, despite avoiding the formation of vitamin A dimers, the retina may nonetheless degenerate due to empty photoreceptors. The absence of therapeutics that can slow the dimerization of vitamin A without

depriving the photoreceptors has prevented elucidating the link between vitamin A dimerization and AMD.

In this protocol, we propose to evaluate a small molecule, ALK-001, that can prevent the vitamin A dimerization without depriving photoreceptors of vitamin A. Using mouse models of retinal degeneration, ALK-001 stops pathological changes of the retinal structure and slows declines in retinal function with age. Therefore, ALK-001 offers an exciting opportunity to clinically test the extent to which the dimerization of vitamin A contributes to AMD. If successful at preventing AMD, and because ALK-001 results from a "minor" chemical change of vitamin A (see below for details), ALK-001 could possibly become widely used in place of dietary vitamin A (vitamin A is exclusively found in food and most dietary vitamin A originates from man-made vitamin A placed in animal diet), similar to Iodine is supplemented in salt or vitamin D in milk. This could help prevent AMD in hundreds of millions of people worldwide, a significant public health impact.

1.5.4.3 Hypothesis

The major hypothesis behind this study is that impeding the formation of vitamin A dimers through daily of administration of ALK-001 will slow the progression of GA associated with AMD.

ALK-001 is an investigational drug that acts as a vitamin A replacement. ALK-001 is a chemically-modified vitamin A, with reduced propensity to dimerize. Because vitamin A dimers have been shown to trigger complement activation, we hypothesize that ALK-001 can also normalize overacting complement that leads to AMD, as was shown in preclinical work [68].

Importantly, ALK-001 is not expected to affect the visual cycle, and therefore avoids visual side effects, such as blurred vision, night blindness, dark adaptation problems, as well as off-target effects that might result from the long-term impairment of the visual cycle. Because of its chemical structure, vitamin A where 3 hydrogens have been selectively replaced with 3 deuterium atoms (see Section 1.5.5), ALK-001 is expected to behave identically to vitamin A and have the same pharmacokinetics and ADME profile. As such, ALK-001 can be administered orally using formulations similar to those found in commercial vitamin A.

1.5.4.4 Proposed Trial: Phase 2/3 study to investigate the long-term safety, tolerability, pharmacokinetics and efficacy of ALK-001 in patients with GA secondary to AMD.

The proposed study aims at expanding our understanding on the role of vitamin A dimers in the progression of forms of retinal degeneration characterized by the presence of vitamin A dimers in the retina. This study will evaluate the extent to which vitamin A dimers contribute to the progression of geographic atrophy secondary to age-related macular degeneration. The study has an 80% power, with a 2-tailed significance of 0.05, to detect a ~33% slowing in the growth rate of atrophic lesions measured between baseline and 24 months (primary outcome measure). Thirty-three percent slowing is approximately twice the amount of slowing judged to be clinically-meaningful by retinal specialists caring for GA patients. The study eligibility criteria were designed to enroll the majority of patients with GA: if one eye must have "pure GA", the fellow eye may have GA, concurrent or history of CNV, or intermediate AMD with one large macular drusen. Estimating that approximately 35% of patients will have CNV in the fellow eye, the study has an 80% power to detect, at 24 months, a 75% reduction in the incidental progression to CNV

in the study eye with a 1-tailed significance of 0.2 (Fisher's exact test).

1.5.5 Investigational Agent (ALK-001) and Regulatory History

The investigational drug ALK-001 (also known as C20-D_3-vitamin A) is vitamin A, whereby 3 hydrogen atoms have been replaced with heavy hydrogen, also known as "Deuterium". Deuterium slows vitamin A's inherent ability to dimerize with itself, thereby preventing vitamin A dimerization.

ALK-001 nonetheless functions virtually identically to non-deuterated vitamin A except in its ability to dimerize: in an ongoing Phase 2 study in Stargardt disease, where 30 subjects receive ALK-001, over 80% of the plasma's vitamin A was replaced with ALK-001's active form within weeks of daily oral administration of ALK-001. After over 12 months of treatment, there were no reports of night blindness or delayed dark adaptation, confirming that deuterated vitamin A can replace and act identically to non-deuterated vitamin A.

1.5.5.1 Pharmacological mechanism of action

Previous work [69, 70] has demonstrated that the rate-limiting step of vitamin A dimerization is the non-enzymatic cleavage of a carbon-hydrogen (C-H) bond on the carbon number 20 of vitamin A. By replacing protium ("hydrogen") atoms of the C20 with heavier deuteriums (D), the C20 carbon-deuterium bonds become harder to cleave than the original C20-H bonds. This result in slowed dimerization, an effect called "kinetic isotope effect".

Deuterium is a naturally-occurring, stable, non-radioactive isotope of hydrogen. About 0.02% of hydrogen atoms are in the deuterium form. The tolerability of deuterium has been demonstrated in multiple studies dating back to the 1930s. For example, in mice replacement of up to 15% of all body water content with deuterated water, i.e. changing H_2O with D_2O, resulted in no toxicity or changes in the animals' health.

Deuterium is also called "heavy hydrogen" because its chemical properties are virtually identical to those of hydrogen, except in chemical reactions where carbon-hydrogens (or carbon-deuterium) bonds are broken. In the case of ALK-001, vitamin A was selectively deuterated at the carbon 20 position, a position known not to be chemically broken during normal vitamin A processing in the body, except when vitamin A forms its toxic dimers. As a result, ALK-001 is expected to behave identically to vitamin A, except for the fact that it should slow dimer formation.

In this clinical trial, a daily dose of ALK-001 contains over 100 times fewer deuterium atoms than deuterium molecules naturally present in the average volume of drinking water consumed daily by an individual. Hence, deuterium atoms contained in ALK-001 are not expected to perturb the amount of deuterium naturally contained in the body.

1.5.5.2 Expected safety and tolerability of ALK-001 in this study

The sponsor is currently running a 24-month Phase 2 enrolling subjects between 12 and 60 years old. As of May 2018, 47 subjects have completed the 12-month visit, 38 subjects have completed the 18-month follow-up visit, and 22 subjects have completed the 24-month visit. ALK-001 has been found to be well-tolerated with no unexpected adverse reaction, clinically-significant

abnormal laboratory values, or any report of night vision changes or dark adaptation problems. The present study is expected to have the same safety and tolerability profile.

The following arguments further speak to the feasibility of the present study:

(1) ALK-001 has the same metabolism as vitamin A: ALK-001 is vitamin A where 3 hydrogen atoms have selectively been replaced with deuterium, to form deuterated vitamin A. Deuterium is a stable (non-radioactive) and naturally occurring (mostly as D_2O in sea water) isotope of hydrogen. Deuterium slows down reactions that involve the cleavage of a carbon-hydrogen bond. Because the carbon-hydrogen bonds that have been changed into carbon deuterium-bonds to form ALK-001 are not cleaved during vitamin A metabolism or usage [71], ALK-001 is expected to behave identically as normal, non-deuterated vitamin A in the body.
(2) ALK-001 behaves identically to vitamin A in the body: In the ongoing Phase 2, over 80% of plasma vitamin was replaced with deuterated vitamin A. No side effects typical of vitamin A deficiency were recorded. If ALK-001 could not carry outs vitamin A's normal functions, one would have anticipated visual side effects (such as difficulty seeing in the dark or night, or difficulty adapting to wide changes in luminosity). In addition, several generations of mice have been given diets containing vitamin A only as ALK-001, and without naturally-occurring vitamin A, with no signs indicating that ALK-001 should behave any differently from vitamin A.
(3) ALK-001 was well-tolerated in a study using the same dose and same duration of treatment proposed here: The tested dose, 14 mg, has been assessed in a Phase 2 study in patients with Stargardt disease and was found to be well-tolerated. Furthermore, higher levels of vitamin A have been previously given for up to 2 years clinical trials, showing an acceptable tolerability profile [72].
(4) Deuterium atoms contained in ALK-001 will not cause biological changes: The number of deuterium atoms in a 14 mg/day dose of ALK-001 is over 100 times smaller than the number of deuterium molecules naturally found in the average volume of drinking water consumed daily.
(5) Unlike beta carotene, vitamin A acetate (ALK-001 parent compound) is not linked to lung cancer in smokers: Beta-carotene, the precursor of vitamin A, has been associated with increased risk of lung cancer in smokers or former smokers [73]. However, vitamin A itself is not associated with such increased risk [74] and as such, there is no need to prevent smokers or former smokers to enroll in this study. A systematic review on the topic can be found here [75].

1.5.5.3 Regulatory History

ALK-001 investigational new drug (IND) application was allowed to proceed in February 2011. A first in human Phase 1a trial was performed between April and September 2014 to assess the safety and pharmacokinetics of ALK-001 taken daily for 4 weeks. A total of 37 healthy volunteers participated in the study. A Phase 2 trial was started in August 2015 to assess the safety, tolerability and effects of ALK-001 in patients with Stargardt disease.

1.5.6 Preclinical Data

A summary of preclinical data is presented in this section; comprehensive information is available

in the investigator's brochure and in four peer-reviewed publications entitled "*C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt's disease*" [69], "*Deuterium enrichment of vitamin A at the C20 position slows the formation of detrimental vitamin A dimers in wild-type rodents*" [76], "*The retina rapidly incorporates ingested C20-D3-vitamin A in a swine model*" [16], and *"Rescue of the Stargardt phenotype in Abca4 knockout mice through inhibition of vitamin A dimerization"* [68]. These non-GLP studies were carried out at Columbia University under the direction of Ilyas Washington, and at Oxford University, under the direction of Robert MacLaren.

In the first publication [69], *Abca4*$^{-/-}$ mutant albino mice, the mouse model of human Stargardt disease, received diets containing either ALK-001 (the treated group) or vitamin A at its natural isotopic abundance ("non deuterated" vitamin A, the control group). The concentration of vitamin A dimers, lipofuscin and other biological markers indicative of ocular health in both groups were measured. Treated mice exhibited an 80% reduction in A2E, a 95% reduction in ATR dimers and a 70% decrease in fundus autofluorescence at three months of age. After six months of treatment, the treated group showed fewer lipofuscin granules as visualized qualitatively by electron microscopy, and at 12 months the mice showed improved retinal function as measured by ERG compared to the control group. Similar reduction (~60%) of A2E accumulation was also observed for mice reared on normal vitamin A diet for 2 months and then switched to diets supplemented with ALK-001 for an additional month.

In work described in the second publication [76], *wild-type* rodents (mice and rats) received a diet containing either vitamin A (control group), ALK-001, or two inhibitors of A2E formation (Fenretinide [65] and TDH [77]). In this study, animals receiving ALK-001 had 45% less A2E compared to age-matched controls. Likewise, animals receiving Fenretinide or TDH had 58% and 40% less A2E respectively, relative to the control group. There was no statistically significant difference in the relative average decrease in A2E among all three inhibitors of A2E biosynthesis.

In the third publication [16], adult swine were fed a diet poor in vitamin A and rich in provitamin A carotenoids. Animals were given orally 3 mg of vitamin A per day, composed of ALK-001 (95%) and non-deuterated vitamin A (5%) mixed in olive oil and filled in a gelatin capsule similar to ALK-001 capsules. Five animals were sacrificed after 2 weeks and another five after 4 weeks. Plasma and tissues were collected at each sacrifice. The ratio of deuterated and non-deuterated vitamin A was determined by mass spectrometry. Results showed that about 85% and 95% of vitamin A was deuterated in the retina after 2 and 4 weeks respectively, indicating that steady state had been reached after 4 weeks. Further, provitamin A carotenoids (such as beta carotene) did not contribute to the vitamin A pool in the retina. Results also showed that the percent of deuterated vitamin A in the plasma closely mirrored that of the retina, indicating that plasma deuterated vitamin A percentage could be used as an indicator for the percentage of deuterated vitamin A in the retina.

In the fourth publication [68], wild-type and *Abca4*$^{-/-}$ pigmented mice were reared on the control vitamin A or treated with ALK-001. Treatment was started or crossed over back to the control diet at various time points. Results showed that replacing vitamin A with ALK-001 impedes the dimerization rate of vitamin A - by approximately fivefold for the vitamin A dimer A2E, and subsequent formation of lipofuscin and normalizes the aberrant transcription of complement genes

without impairing retinal function. Phenotypic rescue by ALK-001 was also observed noninvasively by quantitative autofluorescence in as little as 3 months after the initiation of treatment, whereas upon interruption of treatment, the age-related increase in autofluorescence resumed. Results are in accord with research indicating the contributory role of vitamin A dimers in complement dysregulation.

Several generations of animals have been reared on diets containing vitamin A exclusively under the ALK-001 form (there was no "natural" vitamin A in the diet). There were no abnormalities that could suggest toxicity of ALK-001 or any difference from animals reared on natural vitamin A: animals remained clean, sleek, well-groomed fur, with good skin and mucosal color, alert, socially active, and tended to explore the cage perimeter in all generations.

These preclinical results suggest that administration of ALK-001 may be a rational therapeutic approach to prevent vitamin A dimerization and slow the progression of retinal diseases.

1.5.7 Clinical Data

ALK-001 has been tested in two clinical trials: a Phase 1a, single center, open-label study (NCT02230228), designed to evaluate the safety and pharmacokinetics of various dose levels of ALK-001 administered daily for 4 weeks in healthy adult subjects, and a Phase 2, multi-center, double-masked, placebo-controlled study (NCT02402660), to assess the safety, tolerability, pharmacokinetics and effects of ALK-001 in subjects with Stargardt disease between the ages of 12 and 60 years old.

1.5.7.1 Efficacy

There are currently no human efficacy data. Please refer to preclinical data (1.5.6) for information on scientific rationale, hypothesis, mechanism of action, and efficacy data in mice.

1.5.7.2 Safety

NCT02230228 (completed) and NCT02402660 (ongoing) studies included safety evaluations: adverse events, clinical laboratory tests, 12-lead electrocardiograms, vital signs, physical examination. NCT02402660, which enrolled patients with Stargardt disease further includes ocular tests, such as ocular exams, best-corrected visual acuity (ETDRS), self-reported vision questionnaire, fundus autofluorescence, OCT, microperimetry (optional), and dark adaptation testing (optional). Laboratory tests included the following:

- Biochemistry (Sodium, Potassium, Chloride, Bicarbonate, Urea, Creatinine, Calcium, Total Protein, Bilirubin, Albumin, Alkaline phosphatase, AST, ALT).
- Hematology (WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBC, HGB, HCT, MCV, MCH, PLT).
- Lipid (NCT02402660 only): Triglycerides, total cholesterol, LDL, HDL

Subjects' age ranged from 13 to 62 across both studies. ALK-001 was shown to be well-tolerated in all subjects, at all tested doses, with no unexpected adverse reactions, consistent with the profile of vitamin A. In particular, there was no report of night vision or dark adaptation problems, no serious adverse events associated with the study drug, nor any clinically-significant abnormal clinical laboratory tests. The dose proposed in this study, 14 mg/day, is identical to one of the doses tested in NCT02230228 (for 4 weeks) and NCT02402660 (for up to 2 years). Based on all

data collected to date, administration of ALK-001 in the proposed 2-year study in subjects with geographic atrophy, is expected to be well-tolerated.

1.5.7.3 Pharmacokinetics

Pharmacokinetics (PK) of ALK-001 has been evaluated in detail in NCT02230228. Please refer to the investigator's brochure for detailed information.

ALK-001 PK is measured by following ALK-001's metabolites in plasma. ALK-001 is a deuterated form of vitamin A *acetate*. Vitamin A *acetate* does not circulate in the blood. Instead, vitamin A acetate is metabolized during absorption into vitamin A alcohol (*retinol*), vitamin A esters (such as *retinyl palmitate*), and to a smaller extent *retinoic acid*. Levels of deuterated and non-deuterated retinol, retinyl palmitate and retinoic acid were measured regularly to assess compliance, as well as the replacement of vitamin A with deuterated vitamin A.

Because plasma vitamin A is comprised of retinol and retinyl esters, and because retinyl palmitate represents the majority of retinyl esters (approximately 65-75% [78, 79]), "vitamin A" was approximated as the sum of retinyl palmitate + retinol in plasma.

Total plasma vitamin A (the sums of each deuterated + non-deuterated metabolites of ALK-001) remained on average within known normal physiological ranges. There were no significant changes in the total amount of vitamin A in plasma, indicating that ALK-001 replaces vitamin A with deuterated vitamin A but does not increase the body's total exposure to vitamin A.

Percent deuterated vitamin A in plasma. The percentage deuteration for each metabolite increased significantly between 0 and 2 weeks, and slightly more between 2 and 4 weeks (see figure below). At time 0, subjects who had not taken any ALK-001 had 0% deuterated vitamin A in plasma. At 4 weeks of daily intake, about 80% of vitamin A was deuterated at the 14 mg/day dose. After the treatment was discontinued for a week, this percentage dropped to around 60%. The figure below shows the percentage of deuterated vitamin A over time for three of the tested doses. For the 7 mg and 14 mg doses, we further collected plasma every 4 hours post first- and last-dose, over a 24-hour period.

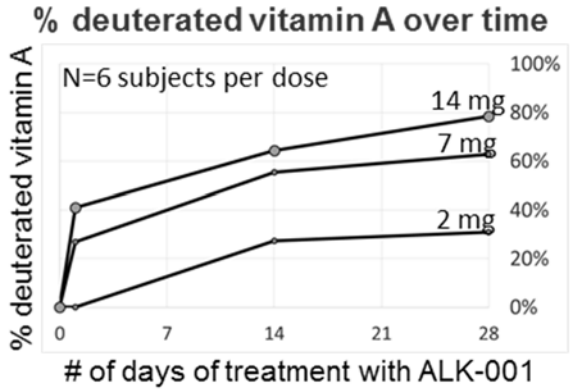


Fig. 1. Percentage of deuterated retinol found in plasma after 1, 14, and 28 days following daily administration of ALK-001 at the shown dose levels.

24-hour PK. 24-hour PK curves indicate that after 4 weeks, plasma levels were close to steady state. Steady state can be defined as the state when one extra dose of ALK-001 transiently increase

the percentage deuteration of ALK-001 metabolites over a few hours post-dose, but the percentage deuteration returns 24 hours post-dose to that at the time of dosing (see curves below). Because 80% or more of the body's vitamin A is stored in the liver and because it takes longer to replace liver reserves, one could expect the percentage of deuterated vitamin A to increase further from this "steady state" as the liver vitamin A is replaced by deuterated vitamin A. Curves shown on the figure below show the 24-hour variations of the % of deuterated vitamin A (vitamin A defined as retinol + retinyl palmitate) following administration of the first (day 1) or the last (day 28) dose of ALK-001 in the phase 1a trial.

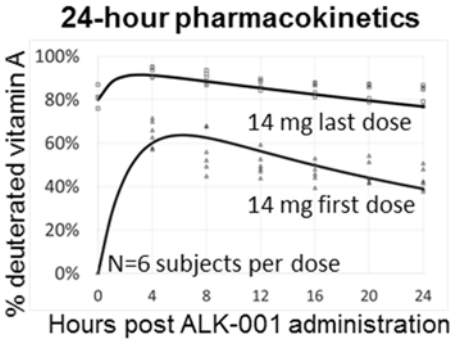


Fig. 2. Figure showing the percentage of deuterated vitamin A (retinol + retinyl palmitate) contained in plasma following the first dose of ALK-001 at 14 mg (lower curve) and following 4 weeks of daily administration at the same dose level (upper curve). Steady state seems to be achieved after 4 weeks. Average plasma vitamin A over a 24-hour period is over 80% for the 14 mg/day group.

1.5.8 Possible Risks and Benefits to Human Subjects

1.5.8.1 Possible Risks

- **Clinical laboratory results**: in an ongoing 2-year study assessing ALK-001 at a dose similar to the dose tested in this protocol, there were no reports of clinically-significant abnormal laboratory values. Nonetheless, vitamin A has previously been associated with mild increases in the following blood parameters, which will be monitored during the study:
  - *Enzyme levels:* ALT, AST and Alkaline Phosphatase.
  - *Lipids:* total cholesterol, triglycerides, HDL or LDL.
  - Clinical significance (see 1.16) will be assessed by the investigator.
- **Side effects and toxicity:** Based on safety data acquired to date in other ALK-001 studies, adverse reactions due to ALK-001 at the proposed dose are expected to be rare in this study. Chronic vitamin A intake is nonetheless associated with various side effects, although many of them are non-specific. It is unlikely that subjects would experience side effects within the first 6 months of treatment. Longer term, the following side effects might be reported:
  - Mild dermatological symptoms including dryness, desquamation or itching.
  - Alopecia, although this is not uncommon in the elderly.
  - Papilledema (optic disc swelling or fuzzy borders), with or without signs of headaches, intracranial hypertension (pseudotumor cerebri), transient visual obscurations (TVO), reports of a more noticeable blind spot, transient nausea, stiff neck, dry skin or lips. Obese female subjects may be more sensitive to vitamin A.
  - Hepatomegaly, sometimes with splenomegaly

  - Other side effects related to chronic vitamin A intake may include: blurred vision, diplopia, anorexia, loss of appetite, nausea, fatigue, cheilitis, angular stomatitis, gingivitis, glossitis, conjunctivitis, peeling, epistaxis (nose bleed), pain of the bones, muscle stiffness, dysuria, exanthema, fever, vertigo, sleep disturbance, edema and swelling.
  - Vitamin A-related side effects or adverse reactions are known to resolve upon discontinuation of vitamin A treatment: therefore, if subjects present with non-tolerable adverse reactions, signs of toxicity, or symptoms which in the opinion of the investigator or sponsor may affect the health of the subjects, these subjects may be asked to temporarily discontinue the study treatment until resolution of the AE or decision by the PI and sponsor to resume treatment (section 1.14.4).
- **Reproductive risks:** Female subjects of childbearing potential will not be allowed to enroll in this study. There is nonetheless a documented risk of birth defects in pregnant females due to chronic intake of vitamin A [80]. At screening, PI may decide to perform or order a pregnancy test, which must be negative before subjects can be randomized. There is no documented increased risk of birth defects for male subjects fathering a child while taking vitamin A. As such, there are no specific contraception requirements for male subjects.
- **Risk of the medical procedures of the study:** The medical procedures involved in the study are all standard procedures already acquired during routine clinical care, and of minimal risk.

1.5.8.2 Possible Benefits

- **Clinically-meaningful slowing of the growth rate of GA**: The study is powered to detect a 33% slowing in the growth rate of atrophic lesions. Survey of retinal specialists indicates that ~18% slowing in the growth rate of GA would be considered clinically meaningful. Here, the study duration of 24 months was chosen to be long enough to measure a clinically meaningful benefit of 33%, while adequately evaluating the long-term safety and tolerability of ALK-001. The dose level was chosen so that 80% of vitamin A would be replaced with deuterated vitamin A after the first four weeks of treatment. Eighty percent replacement is expected to be therapeutic.
- **Slowing of the progression from GA to CNV:** The study is further powered to detect a 75% slowing in the progression from GA to CNV in the study eye, when the fellow eye has CNV. When the fellow eye has CNV, natural history data indicate that the incidence of CNV in the GA eye is approximately 10% per year. Because vitamin A dimers trigger angiogenesis, stopping the formation of vitamin A dimers could slow the progression to CNV of the GA eye.
- **Slowing of visual acuity or reading speed loss:** Visual acuity is not an appropriate primary outcome measure in most geographic atrophy studies, as the atrophy continues to degenerate in the retina, while visual acuity only indicates the health of a small portion of the retina. Nonetheless, visual acuity is known to progress at a rate of approximately 3-5 lost letters per year on the ETDRS chart, and the eye with better visual acuity is known to progress faster [81]. Subjects enrolled in this study must have better than 20/200 visual acuity and are expected to have on average ~20/40-20/100 visual acuity at baseline. By slowing the growth rate of atrophy, we may be able to slow decreases in visual acuity or reading speed. Therefore, visual acuity and reading speeds will be measured.

1.5.9 Significance of the proposed trial

There are no approved treatments for Geographic Atrophy, a condition that leads to legal blindness in almost all cases. Ongoing industry-sponsored clinical trials are investigating compounds injected intravitreally and targeting the complement pathway. Clinical trials to date targeting the complement have been inconsistent. As such, there is a need for an orally-delivered compound and testing a different mechanism of action.

An oral therapy has the advantage of being convenient for patients and physicians. In addition, because of its delivery mechanism and expected safety and tolerability, ALK-001 could in the future be tested in earlier stages of AMD, especially patients with intermediate AMD, as a prophylactic or disease-modifying agent to slow or prevent the progression of AMD to its advanced forms, GA or CNV.

Clinical data to date indicate that daily administration of ALK-001 at 14 mg/day in patients between 18 and 60 years old is safe, well-tolerated, and replaces over 80% on average of vitamin A with deuterated vitamin A. In the present study, we aim at acquiring safety, tolerability and pharmacokinetic data in patients aged 60 years old and over, and to measure the extent to which slowing vitamin A dimerization ~4-fold slows the progression of GA lesions.

1.6 STUDY OBJECTIVES

1.6.1 Primary Objective and Primary Outcome Measure (Endpoint)

Primary objective:

- To assess the effects of ALK-001 on the growth rate of GA lesions after 24 months of treatment in patients with GA associated with AMD.

Primary outcome measure (endpoint):

- Growth rate of the area of atrophic lesions between baseline and 24 months, as measured on fundus autofluorescence (FAF) imaging and verified by optical coherence tomography (OCT).

Methods of data analysis will be detailed in a Statistical Analysis Plan (SAP) prior to the performance of unmasked analyses. The SAP shall supersede this protocol in case of discrepancies with the SAP. The SAP shall also be submitted to the regulatory agencies before any unmasked analyses are performed.

1.6.2 Secondary Objectives and Secondary Outcome Measures

Secondary objectives of the trial

- To assess the safety and tolerability of ALK-001 in patients over 60
- To assess the pharmacokinetics of ALK-001 in patients over 60
- To assess the effects of ALK-001 on the growth of GA lesions after 12 months of treatment
- To assess the effects of ALK-001 on the growth of GA lesions between 6 and 24 months of treatment
- To assess the effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has CNV

- To assess the effects of ALK-001 on visual function, including BCVA, LLVA, reading speed, questionnaires on quality of life and vision.

Secondary outcome measures (endpoints)

- Safety and tolerability assessed by frequency and severity of Adverse Events (AE) and Serious Adverse Events (SAE), as reported by patients or clinically-significant findings on 12-lead ECG, physical exam, ocular exams, retinal photographs, clinical laboratory tests, bioanalytical tests (vitamin A), BCVA
- Pharmacokinetics assessed by assessing the percentage of deuterated vitamin A
- Growth rate of GA lesions after 12 months as measured on FAF imaging and verified by OCT
- Growth rate of GA lesions between 6 and 24 months as measured on FAF imaging and verified by OCT
- Incidence of CNV in the study eye with GA, as assessed by PI using standard of care practice: fluorescein angiography (FA), or OCT angiography (OCTA)
- Changes in BCVA
- Changes in LLVA
- Changes in reading speed as measured by MNREAD and IREST
- Changes in quality of life, visual function or functional vision, as measured by Visual Function 14 (VF-14), Functional Reading Independence (FRI), and Macular Disease Dependent Quality of Life (MacDQOL)

1.6.3 Exploratory Objectives and Exploratory Outcome Measures (Research Only)

Exploratory objectives and exploratory outcomes

- To assess the effects of ALK-001 on retinal anatomy
  - Evaluation of photoreceptors and RPE layers on SD-OCT imaging. Specifically, evaluation of RPE, ellipsoid zone (EZ) band (also known as IS/OS junction layer) and outer nuclear layer (ONL)
- To assess the effects of ALK-001 on retinal function:
  - Changes in retinal sensitivity as measured by fundus-tracking microperimetry
- Effects of ALK-001 on drusen characteristics
  - Changes in drusen volume as measured by SD-OCT
- Effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has intermediate AMD
  - Incidence of CNV in eyes with GA, as assessed by PI using standard of care (FA or OCTA)
- Effects of ALK-001 on the incidence of advanced AMD (CNV or GA), when the fellow eye has intermediate AMD
  - Incidence of advanced AMD in the fellow eye, as assessed by PI
- Distance of Preferred Retinal Locus (PRL) to foveal center and other fixation characteristics
  - Changes in fixation characteristics as measured by fundus-tracking microperimetry
- Association between ALK-001 treatment effects and genetics
  - Stratification of effect size by mutations on a panel of genes

- Association between ALK-001 treatment effects and complement
  - Stratification of effect size based on subject's complement function and complement blood levels

1.7 STUDY DESIGN AND RATIONALE

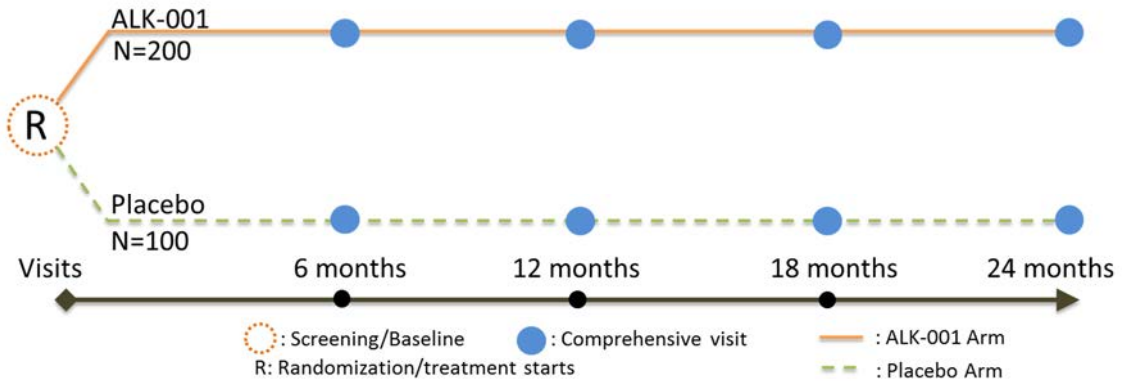
1.7.1 Overview of Trial Design

This is a randomized, double-masked, parallel-group, multicenter study evaluating the safety and efficacy of ALK-001 in subjects with GA secondary to AMD. Approximately 300 subjects who match all eligibility criteria will be randomized to receive either ALK-001 (n = 200) at 14 mg/day or placebo (n = 100) for 24 months. After 24 months of treatment, an optional open label extension is planned to determine the lowest chronic dose that can maintain approximately 80% of deuterated vitamin A in plasma.

The expected total duration of the study from first patient first visit to last patient last visit, excluding the optional open label extension is 2 years and 9 months, which includes a total of up to 2 years of treatment with the study drug and 9 months of enrollment. Subjects, investigators and study staff, and sponsor staff who may be in contact with investigators or subjects, will be masked for the duration of the study.

Safety and tolerability will be assessed by monitoring AEs, clinical laboratory tests, vital signs, ECG and physical examinations. The primary endpoint for assessment of efficacy is the growth rate of GA lesions measured on FAF imaging and confirmed by OCT, between baseline and 24 months of treatment. Secondary efficacy endpoints include effects of ALK-001 on visual and ocular function and anatomy, as measured by questionnaires, BCVA, reading speed, and OCT. Exploratory outcomes measure include microperimetry and assessment of complement in the blood.

Protocol waivers, exemptions or deviations are not allowed with the exception of immediate health risk concerns, or to the extent allowed in specific sections of this protocol. Adherence to the study design requirements is essential and required for study conduct. Subject's health will be monitored through the end of the study. An independent Safety Monitoring Committee (SMC) will be commissioned to review unmasked safety data. All assessments will be performed according to the Events Table (1.2). A diagram of the study design and timelines is provided below.



1.7.2 Study Design Rationale

The study is designed to generate long-term safety and efficacy data for the administration of 14 mg/day of ALK-001 in subjects with GA secondary to AMD and otherwise deemed healthy to participate in the study.

1.7.2.1 Study Population

The study population comprises subjects 60 years old and over at the time of screening or at randomization, who are treatment-naïve to ALK-001 and have been diagnosed with geographic atrophy secondary to age-related macular degeneration in at least one eye. Subjects should be healthy otherwise, although benign conditions are acceptable if they are not likely to affect the subject's health, interact with the treatment, or confound the evaluation of safety, tolerability, or effects of ALK-001.

1.7.2.2 Dose Levels

A high percentage of deuterated vitamin A is recommended to demonstrate efficacy: ALK-001 is designed to replace normal vitamin A. The greater this replacement in the retina, the more efficacious ALK-001 will be at slowing the dimerization of vitamin A. Because measuring vitamin A in the retina is not directly accessible, collaborators have used an adult swine model to demonstrate that the percentage of deuterated vitamin A in plasma mirrors that of the retina [16]. Thus, the percentage of deuterated vitamin A in plasma can be used as an indirect measure of the percentage of deuterated vitamin A in the retina.

Greater than 80% replacement of vitamin A with deuterated vitamin A is achievable: The percentage of *deuterated vitamin A* should preferably be over 80%, so that most vitamin A is in the deuterated form during the study. In mice models, ALK-001 prevented age-related declines in retinal function when as little as ≈ 80% of the vitamin pool was deuterated vitamin A (ALK-001's active metabolite) [70]. Eighty percent deuterated vitamin A resulted in greater than ≈ 4-fold reduction in the rate of dimerization. Data from a Phase 1 clinical trial indicate that a daily intake of 14 mg of ALK-001 is sufficient to replace 80% of deuterated plasma vitamin A in humans, with no major dietary restrictions. These data were confirmed in a Phase 2 study in Stargardt disease. In this phase 2, an additional, higher dose level was also tested. Data indicate that there would not be a higher benefit from using this higher dose. As such, only one dose is being tested in this study.

Using the 14 mg/day dose, the total intake of vitamin A (combining natural vitamin A from dietary sources + ALK-001 dose) is expected to be safe and well-tolerated for the 2-year treatment period: Daily intakes of vitamin A of ~100 mg (300,000 IU) for 1 year followed by ~50 mg (150,000 IU) during the second year were well-tolerated in a phase 3 cancer clinical trial enrolling close to 1,300 patients aged 23 to 83 years old [82] although some grade 3 and 4 toxic adverse events were observed. The degree of tolerability is usually higher in cancer trials. In another trial, daily dosing of 129 patients with sun-damaged skin for up to one year at doses up to ~25 mg (75,000 IU) of vitamin A has showed acceptable tolerability [72], while doses below ~8 mg (25,000 IU) have been shown to be relatively safe for decades [83]. Other trials testing vitamin A include a breast cancer trial testing ~100 mg per day (300,000 IU) for up to 2 years [84].

In ALK-001 Phase 2 study, we have found that a daily administration of ALK-001 was well-

tolerated, with no unexpected adverse reactions. It is important to note that vitamin A-related adverse reactions are known to resolve upon discontinuation. As such, if during the study any patient experiences signs or symptoms of hypervitaminosis A, which would place the patient at risk of continuing the study, such patient shall temporarily discontinue the study drug. See section 1.5.8.1 for details.

In the present study, we propose to assess the safety and efficacy of daily intake of 14 mg/day of ALK-001 for a period of 24 months. After 24 months, lower chronic doses will be assessed to determine the lowest dose that maintains ~80% deuterated vitamin A in plasma.

1.7.2.3 Treatment Groups

Subjects will be randomized to placebo or to ALK-001 at 14 mg/day.

Based on all mechanistic, preclinical and clinical information available to date, 14 mg/day is likely to be therapeutic, as it will replace over 80% of vitamin A with deuterated vitamin A, which would be expected to slow the dimerization process over 2-fold in the retina. For percentages around 90% of replacement, dimerization is slowed 4-5 fold.

Considering the safety of the 14 mg/day dose, as demonstrated in previous studies, there is little scientific reason to explore a lower dose in the initial treatment period of 2 years, at it would increase the chance of type II error but would not be expected to increase safety in a clinically-meaningful way.

1.7.2.4 Route of delivery, frequency & time of dosage

Oral route preferred for ALK-001: The oral route is preferred as the retina is difficult to reach with topical formulations that might also be inconvenient (eyedrops, intravitreal injections). Vitamin A can be taken orally and is naturally transported to the retina via retinol binding proteins (RBP) at physiologically relevant and controlled levels.

Once daily dosage preferred: Once daily dosing is recommended in this study based on pharmacokinetic data from vitamin A and data obtained in Phase 1. Subject will be advised to take their daily capsule at the same time each day, preferably at the same time they take their other medications if any.

1.7.2.5 Duration of Treatment

This study is designed to evaluate the safety and tolerability profile of ALK-001 in subjects over 60, and to determine the efficacy of ALK-001 on the progression of geographic atrophy.

The initial treatment period will end when the last subject completes the last scheduled visit.

A 2-year open label extension is planned to explore chronic maintenance dosing, as well as long term efficacy in case 2 years would not be sufficient to show an effect. Subjects who complete the initial treatment period may be offered to continue treatment, with a possible interruption between the first 2 years of treatment and the open label extension. Details of the extension period may be provided in future protocol amendments.

1.7.2.6 Study Control, Randomization and Masking

To prevent or reduce bias, a placebo will be used. This is particularly important as endpoints such as best-corrected visual acuity, measurement by the study team or reading center of RPE lesion atrophy, or microperimetry testing can be influenced with bias. Placebo will also be used to assess safety and establish the type, severity and frequency of adverse events associated with the drug.

Treatment masking will be in place to further reduce bias during data collection and analysis. Randomization will ensure there is no bias in the assignment of subjects to treatment groups, and to enhance the validity of statistical comparisons across treatment groups. No stratification will be used.

Investigators and clinical staff, subjects and all sponsor personnel having contact with the study sites will remain masked to the treatment allocation for the duration of the study. The labels on the packaging of the study drug only indicate a random medication number (eg: "CA27") and not the actual treatment assignment. All capsules weigh, look, smell and taste the same.

Unmasking of certain personnel when necessary for some data analyses, will require sponsor's approval and will be clearly documented.

1.7.2.7 Safety Evaluations

Based upon vitamin A's known safety and tolerability profile, possible AEs of interest have been identified and will be monitored during this study (see section 1.5.8.1). Safety data will be acquired by: 12-lead ECG, physical exam, ocular exams, clinical laboratory values, BCVA, OCT, FA, OCTA, and FAF.

To make sure that any potential for hypervitaminosis A is detected, adverse reactions such as headaches, nausea, dry lips, dry skin, signs such as papilledema (optic disc swelling), and clinically meaningful changes in clinical laboratories will be explored. Any clinically significant level will be reported as an AE (see section 1.16.1.4). In addition, levels of retinol, retinoic acid, and retinyl esters will be measured periodically. In order to avoid study unmasking, such data will be reviewed by the SMC. See section below on pharmacokinetic evaluations.

Vitamin A-related adverse reactions are usually reversible upon discontinuation of the vitamin.

1.7.2.8 Pharmacokinetic Evaluations

Plasma will be collected to measure compliance and further assess the pharmacokinetic profile of ALK-001, how it might be influenced by dietary vitamin A intake, how it fluctuates over a 2-year period as liver stores are turned over, and how the percentage of deuterated vitamin A in the blood might be linked to the progression of GA.

Metabolites of vitamin A measured in this study: ALK-001 is expected to replace existing, non-deuterated vitamin A. Total vitamin A in the plasma will be approximated by the sum of retinol + retinyl palmitate. Deuterated retinyl palmitate peaks 4-hours post ALK-001 dose then rapidly returns to levels close to baseline levels 24 hours post-dosing. Deuterated retinol increases more slowly to peak 8-12 hours following dosing and decreases more slowly over time. Retinoic acid, another vitamin A metabolite, with direct function on vision, will be measured. The absolute levels

and percentage deuteration of retinol, retinyl palmitate and retinoic acid will be measured. Percentages are calculated as the ratio between the deuterated analyte and the total amount of each analyte. Total amounts of each analyte will be calculated as the sum of the deuterated and the non-deuterated analyte. Absolute levels above the upper limit of normal may not indicate toxicity in the absence of clinical signs or other clinically meaningful laboratory abnormalities.

In this trial, levels of each analyte are expected to remain within the following ranges, considered normal based on a review of the literature:

Analyte (total deuterated + non-deuterated)	Approximate upper limit of normal
Retinol	1,500 ng/mL
Retinyl palmitate (random)	5,000 ng/mL
Retinyl palmitate (12+ hour after dosing)	500 ng/mL
Retinyl palmitate (24+ hour after dosing)	200 ng/mL
Retinoic acid (random)	5 ng/mL

1.7.2.9 Efficacy Evaluations

Effects of ALK-001 on the progression of GA will be evaluated using fundus autofluorescence imaging. Although atrophic lesions can be readily measured using FAF imaging, OCT imaging will be used to confirm that the measured areas are indeed atrophic regions of the retina.

In addition, other measures of efficacy will be explored, by measuring the following variables:

- Incidence of CNV,
- BCVA,
- Reading speed,
- Visual questionnaires,
- Microperimetry (wherever available).

1.7.2.10 Complement and Genotype

We propose to explore the association between each subject's response to ALK-001 and their complement status, as determined by *genetic polymorphisms (SNPs)*, *serum levels*, and complement *function (*synonym of *"activity")*. We are interested in complement because vitamin A dimers are known to activate the complement cascade [20, 30]. We have also shown that inhibiting dimerization in mouse leads to normalization of the transcription of genes involved in the complement [85].

The complement system comprises approximately 20 proteins synthesized by the liver and the RPE [86]. AMD risk is strongly associated with DNA variants for the genes encoding for complement system proteins. For example, complement factor H (CFH) itself is strongly associated with AMD [53-56], with a single common variant explaining ~43% of AMD risk in older adults. Common genetic variants in complement component C3, Factor B, C2, and Factor I also confer a risk for the disease [87]. In contrast, certain mutations spanning CFH, confer protection from developing AMD [88, 89]. Genetic testing can give information about the risk of developing AMD, but to date there have been no solid associations between genetic mutations and severity of geographic atrophy progression, or response to therapeutic intervention [90-92]. To

address this shortcoming, this study will carry out genetic testing and quantification of serum complement proteins, and in addition, test the actual function (see table below) of the complement system in each patient, as genetic variants may result in differences in complement function even in absence of gene expression differences. As complement function is constant over time [93, 94], and complement is expected to function similarly in the retina, complement function in the plasma will be measured using the commercial CH50 and AH50 tests.

We suspect that vitamin A dimers, which form on the surface of the phospholipids of the disk membranes, modify disk membranes in ways that activate complement. Such complement activation caused by vitamin A dimer-modified disk membranes would explain data linking vitamin A dimers to complement. Such a scenario would also predict that patients whose complement system reacts more strongly to dimers-altered disk membranes, would most benefit from preventing such alteration through administration of ALK-001. We thus plan to evaluate complement status as a means to predict the extent to which patients may benefit from ALK-001. We will search for a correlation between complement serum levels and/or genetic polymorphisms of approximately 20 AMD-associated genes, and/or, complement function with treatment effects as measured GA growth rates.

Accordingly, we will collect serum samples from participants and test:

(1) Complement *function* will be measured using two commercial assays:

Test Name	Notes	Range	Ref.
Complement, Total, function (CH50)	Measures the ability of the membrane attack complex to form and lyse altered liposomes decorated with foreign dinitrophenyl groups.	30-75 U/mL	[95]
Complement, Alternate (AH50)	Activates serum then quantifies formation of the C5b-9, membrane attack complex, via the alternative pathway	>46%	[96]

(2) Complement *serum levels* of C3d, Ba, C3a, C5a, SC5b-9, C3, C4, factor B, factor H and factor D will be quantified.

(3) *Complement genetic polymorphisms (SNPs)* of 20 genes associated with AMD will be tested by Fulgent Diagnostics, a CLIA certified lab. The genes include: ABCA4, C2, C3, CFB, CFH, CFI, CNGB3, CST3, CX3CR1, EFEMP1, ELOVL4, ERCC6, FBLN5, HMCN1, HTRA1, PRPH2, RAX2, RLBP1, RPGR, TLR4, which are all part of the standard Fulgent "AMD panel", as well as ARMS2 individually. Additional genes may be added to this list.

We will compare 1) Complement *function; 2)* Complement *serum levels and 3) Complement genetic polymorphisms (SNPs)* with rates of GA growth as determined by FAF, in order to determine the extent to which any of these variables is predictive of which AMD patients will benefit most from ALK-001.

1.7.2.11 Avoidance of vitamin A supplements and liver products during the trial

Because ALK-001 is used to replace vitamin A, any overly high intake of dietary vitamin A will reduce the activity of the drug. Study participants should avoid taking items that are overly high in vitamin A, which includes vitamin supplements containing vitamin A or beta-carotene and liver-

based food or liver oil products for the most part. Consumption of fruits and vegetables is not restricted. See section 1.11.2 for details.

1.8 SUBJECT SELECTION

1.8.1 Inclusion Criteria

A prospective subject will be eligible if he/she meets **all** the following inclusion criteria at screening or at randomization (as applicable), except upon sponsor's approval which shall be documented:

General inclusion criteria:

1. Male or female 60 years and older.
2. Healthy as judged by investigator.
3. Has signed and dated the informed consent form.
4. Is able and willing to perform the study procedures.
5. Is able and willing to comply with the schedule of the study visits.
6. Is able and willing to self-administer the study drug.
7. Is able and willing to follow the instructions and comply with the avoidance of vitamin A supplements.
8. Is likely to complete the 2-year study as judged by the investigator.

At least one eye, designated as the "study eye", must meet all the following inclusion criteria:

9. Study eye displays well-demarcated GA lesion(s) measuring a total area between approximately 1.5 sqmm and 20 sqmm, measured on fundus autofluorescence imaging (FAF), as confirmed by sponsor or designee.
10. Study eye presents hyperautofluorescent borders in the junctional zone of GA, as confirmed by sponsor or designee.
11. If GA lesions are multifocal in the study eye, one lesion at least must be approximately 1.00 sqmm or greater.
12. In case of foveal sparing, the smallest distance between GA border and foveal center must be under approx. 250 µm.
13. All GA lesions in the study eye must fit entirely within the 30-degree retinal imaging field centered on fovea.
14. Study eye has ETDRS BCVA of 33 letters (~20/200) or better.
15. Study eye has clear or adequate ocular media and pupillary dilation, including no allergy to dilating eyedrops, to permit good quality retinal imaging as judged by the investigator.

The non-study eye, designated as the "fellow eye", must meet all of the following inclusion criteria:

16. Fellow eye presents with one of the following features: (a) reticular pseudodrusen (RPD), (b) intermediate AMD with at least one macular drusen greater than approximately 125 µm in diameter, (**c**) active or history of CNV, (**d**) geographic atrophy with or without a history of, or concurrent CNV.

1.8.2 Exclusion Criteria

A prospective subject will **not** be eligible if **any** of the following criteria apply at screening or at randomization (as applicable), except upon sponsor's approval, which shall be documented:

General exclusion criteria:

17. Active or historical medical condition (systemic or ophthalmic), which in the opinion of the investigator, may prevent performance of study procedures, compliance with the protocol, or continuous participation of the subject throughout the 2-year duration of study.
18. Currently taking or has taken medications associated with retinal toxicity, except for short durations as judged by investigator.
19. Is currently taking oral retinoids or medications that might affect absorption, metabolism, or function of vitamin A.
20. Has participated in any drug or device trial within 60 days of randomization.
21. Anticipates participating in any other drug or device trial over the next 2 years.
22. Is hypersensitive or allergic to fluorescein.
23. Has clinically-significant abnormal laboratory result(s) at screening, which in the opinion of the investigator, makes the patient unsuitable for study participation.
24. Has clinically-significant abnormal physical exam finding(s) at screening, which in the opinion of the investigator, makes the patient unsuitable for study participation.
25. Has active or historical, acute or chronic, liver disorder except when benign.
26. Has a clinically-significant cardiac abnormality, a clinically-significant abnormal ECG, or a marked prolongation of QTc at screening (>460 msec for male or >480 msec for female, approximately).
27. Female of childbearing potential, pregnant, lactating or positive serum pregnancy test at screening.

Study eye exclusion criteria:

28. Study eye has historical or active CNV.
29. Study eye has myopia of -6 diopters or more approximately, except if retinal imaging can be properly focused.
30. Study eye has GA thought or proven to be caused by any condition other than AMD.
31. Study eye has GA lesions expected to (i) expand larger than the imaging field of view, or (ii) merge with other retinal features (optic disc or peripapillary atrophy, other non-AMD atrophic lesions, etc.) during the 2 years of the study.
32. Subject, in the case of a systemic treatment, or study eye, in the case of a monoocular treatment, has previously received treatment, surgery or procedure for GA or AMD, including clinical trials, except when there is documented evidence that the subject was receiving placebo or was part of a sham group.
33. Study eye has active or history of ocular disorder, which may confound assessment of the retina morphologically or functionally, as judged by investigator.
34. Study eye has active or history of glaucoma, uncontrolled elevated intraocular pressure, retinal detachment, RPE tear, recurring uveitis, retinal vein occlusion, diabetic retinopathy, diabetic macular edema.
35. Study eye has history of submacular or intraocular surgery, vitrectomy, or device implantation (except IOL).
36. Study eye has received intravitreal injections or cataract surgery within 90 days of randomization.
37. Study eye is expected to require cataract, epiretinal membrane, or ocular surgery over the next 2 years as judged by investigator.

NOTE: PI shall make the final determination regarding all eligibility criteria.

1.8.3 Study Requirements, Restrictions and Instructions for Subjects

Investigator should enroll participants they believe will follow the study requirements and be likely to complete the 24-month treatment period. Investigators shall discuss with prospective and enrolled subjects about the importance of the study requirements outlined below. Subjects must be willing and able to continuously adhere to the study requirements throughout the duration of the study. Non-compliant subjects will be withdrawn from the study and have to discontinue the study treatment. Details about each of the below requirement are found in the corresponding section.

1. **Adherence to visit schedule**: subjects will be informed about the schedule of all future visits and should ensure they have the time to participate in the 24-month study, and the resources to travel to/from the sites. Missed visit may result in withdrawal.
2. **Study procedures**: subjects should be informed of which study procedures will be performed.
3. **Compliance with study drug intake**: subjects should be informed before the study, and reminded during the study, to take the drug daily for 24 months, preferably at the same time every day and at the same time they take their other medications, unless prescribed otherwise by the investigator.
4. **Subjects must not consume dietary supplements containing vitamin A, liver-based products, or foods known to contain excessive amounts of vitamin A** (section 1.11.2).
5. **Subjects should not take any medications prohibited under this protocol,** except when medically indicated, for the duration of the study (section 1.11.3).
6. **Subjects must not enter into any other investigational drug or device** clinical study, unless deemed medically necessary by the PI and sponsor.

1.8.4 Exemptions to Entry Criteria

Subjects must be compliant with all inclusion and exclusion criteria, unless explicitly permitted in writing by sponsor. Such deviation should only be permitted if it would not be of clinical or scientific significance and would have no significant effect on the results of the study. The exemption should be documented in the source documents and correspondence (including oral notes) recorded in the regulatory binder.

1.9 STUDY DRUG ADMINISTRATION AND MANAGEMENT

1.9.1 Treatment Groups

Subjects will be considered "enrolled" when they are determined to have met all eligibility criteria **and** after they are randomized to a treatment group. Subjects will be randomized 2:1 to 14 mg/day of ALK-001 or placebo. The treatment period will last for up to 24 months and subjects and investigator will be masked to treatment group.

1.9.2 Timing of study drug intake

a) Subjects will be instructed to take one capsule per day, by mouth, at a time of the subject's preference, usually at the same time they take their other daily medications.
b) Subjects will be instructed to take the study drug at approximately the same time each day.
c) Time of usual study drug intake, duration elapsed since last study drug intake (at the time blood samples are collected during follow-up visits), and whether the capsule is taken before, after or during a meal should be recorded.
d) If subjects are taking their study drug in the morning, subjects should not take a dose on the morning of a follow-up visit. Instead, they should wait until after blood collection is completed for that visit to take that day's dose.

1.9.3 Missed Dose

a) Subjects should avoid missed doses.
b) If a subject forgets to take a dose, they should take the missed dose as soon as they remember it, even if that means taking 2 doses on the same day.
c) Subjects should not take more than 2 capsules in one day.

1.9.4 Method of Assigning Subjects to Treatment Groups

Randomization: Only after receiving authorization to do so by the sponsor, investigator will randomize subjects who are confirmed to meet all entry criteria at screening and continue to meet those criteria on day of randomization. Randomization consists in assigning a medication ID to a subject and to dispense the study medication, usually at the same time. Subjects are allocated a treatment based on random, permuted block sizes. Blocks are randomly selected from a size of 3 or 6.

Errors in Medication ID assignment*:* If a subject is assigned a medication ID in error and has not started treatment, the error shall immediately be corrected and documented, so that the subject receives the medication he/she was supposed to receive.

If a subject has already been dispensed and has already taken one capsule of the wrong medication ID, the drug dispensed medication ID shall now prevail and should replace the medication ID originally intended to be dispensed. However, no two subjects shall be assigned the same medication ID, and if a dispensing error has been made, the subject receiving the wrong medication shall be informed to immediately stop taking the wrongly provided medication, to return all provided medication, and to start receiving the proper medication. Randomization date shall be adjusted to the date at which the subject started the proper medication. A note should be added to the source documents to explain the discrepancy.

Process*:* A randomization list is used to identify which medication ID to dispense to the subject about to be randomized. The investigator must pick the next medication ID available at the clinical site, by following the order on the masked randomization list which will be distributed to the investigator at the start of the trial. The sponsor will be responsible for shipping out drug supplies to each site. To ensure proper drug supply is at each site, investigators should inform the sponsor in advance of subjects' scheduled randomization visits, so that sufficient drug supply is already at

the site on the scheduled day of the patients' randomization visit. An online randomization portal may also be used, in place of the paper randomization list.

Once randomized, subjects will immediately receive their first study medication bottle either through the PI or designated personnel, through the site pharmacy, or directly by mail. If received by mail, subjects will be requested to confirm receipt, which shall be documented.

Randomization code, randomization list (or schedule): A randomization code, used to prepare the randomization list, will first be prepared by the sponsor. The code will be programmed so as to be reproducible if the need arises. Once approved, this code will be tested by the sponsor to generate a dummy randomization list for quality control. Once the code has been verified to work properly, an unmasked vendor/consultant designated by the sponsor will generate the final randomization lists (masked and unmasked). The *unmasked* randomization list will be accessible to select persons only (SMC members, unmasked statistician(s), label printing company, packaging company, other unmasked vendors). The investigator and the sponsor will receive a copy of the *masked* randomization list which will contain the sequence of medication IDs, but not the actual treatment allocation nor any information about blocks order or size. Any further instructions for randomization will be provided separately.

1.9.5 Treatment Allocation

To assure even treatment balance and minimization of bias, subject allocation to treatment group will be determined using random permuted block randomization, without stratification. The following tables summarize the expected enrollment:

Treatment Group	Total
Placebo	100
14 mg/day	200
Total	300

1.9.6 Dose Modification or Interruption

Except when authorized by sponsor or as permitted in other sections of this protocol, modifications of the study drug dosage are prohibited, including if subject has received the incorrect drug dose by mistake. If study drug dosing must be discontinued (see 1.14.4), the subject may be withdrawn from the study after discussions with the sponsor (see 1.14.6).

1.9.7 Masking / Unmasking

1.9.7.1 Masking to Treatment Assignment

Subjects, site personnel, pharmacy personnel, monitors and sponsors will remain masked to the treatment assignments throughout the study. The below list provides a list of personnel and whether they should be masked to treatment ("M") or unmasked to treatment ("U"). If necessary for the conduct of the study, this list might be amended by the sponsor and if so, will be documented in the regulatory binder. The list of persons authorized to receive unmasked data/treatment code may be amended from time to time by the sponsor.

	Treatment assignment	Bioanalytical data
Sponsor personnel with direct or indirect access to clinical data	M	Available, masked to treatment and subject ID
Site clinical staff (including PI, sub-I, coordinator)	M	Available, masked to treatment and subject ID
Site pharmacy (if applicable)	M	-
Monitor	M	Available, masked to treatment and subject ID
Central Lab	M	-
Reading Center (Retinal Imaging)	M	-
Bioanalytical laboratory	U	U
Study drug supply management designee	U	-
Quality assurance person / Unmasked monitor	U	U
SMC	U	U
Statistician preparing unmasked analyses	U	U
Designees preparing randomization list	U	-

- does not have access to data
M masked to treatment
U unmasked to treatment

1.9.7.2 Masking to PK data

For each subject in the trial, the bioanalytical lab or an unmasked person may generate and assign a random subject PK ID # to each subject (which will be different from the medication ID # or the actual subject ID). This is to mask the subject ID from the clinical team and sponsor, but still be able to provide individual masked data masked personnel.

Full, identifiable results containing subject IDs, site, treatment allocation, or blood collection date can only be provided to authorized personnel, which shall include at least the SMC, statisticians and unmasked personnel designated by the sponsor.

Sponsor and investigators should be allowed to review PK data on an-ongoing basis as long as such data does not enable treatment unmasking. The bioanalytical lab or a designated unmasked person will be in charge of reviewing the PK data and/or providing a redacted version to the sponsor and investigators.

For that, all pharmacokinetic data and treatment assignment (dose vs. placebo) will be made available, but will not contain the subject's identity (i.e. subject ID number, medication ID#), nor the dates of visit, specific site, or any other information that could result in unmasking or partial unmasking of the treatment allocation. The table should contain the masked subject PK ID. Furthermore, datasets shall be provided only bulk following the randomization block, or as determined appropriate by the statistician. Special precautions should be taken after subjects are

withdrawn from the study, or for subjects with missed data/visits to avoid unmasking. Such precautions shall be put in place by the designated person providing the data to the sponsor and investigators.

Hypothetical example of bioanalytical table that can be sent to masked personnel:

Subject ID	Subject PK ID	Collection Date	Collection Time	Retinol Conc. (ng/mL)	Retinol-d_3 Conc. (ng/mL)	Visit
[redacted]	001	[redacted]		380	0	V01
	001			80	400	V03
	001			40	450	V04
	002			520	0	V01
	002			80	450	V03
	002			35	500	V04

1.9.7.3 Unmasking of individual study subjects in case of medical emergency

The code linking treatment to medication ID will be maintained (i) by the labeling company, (ii) by the unmasked statistician(s), to allow the investigator to break the masking for an individual subject solely in the case of a medical emergency or necessity.

Unmasking: **Code breaks must occur only when specific knowledge of the treatment group (treatment or placebo) would dictate the treatment or course of action to follow to manage the subject's medical emergency or necessity**.

In the event a code break must occur, the investigator will first contact the sponsor prior to unmasking (Contact details found on cover page). For life-threatening serious adverse event only, and if the investigator has been unsuccessful in contacting the sponsor, the investigator may proceed with unmasking the subject without first notifying the sponsor by following unmasking instructions provided in the study binder. The investigator must then notify the sponsor within 24 hours of breaking the code. Information pertaining to all circumstances that resulted in unmasking, such as reason, date and time, shall be clearly recorded in the subject's source documents. In addition, the sponsor may also for matters relating to health risk concerns, unmask individual subjects at any time.

After unmasking: After unmasking of a particular subject, the subject should permanently discontinue the treatment and be withdrawn. In addition, the nature of the treatment (treatment or placebo) should be stored in a sealed, labeled and signed envelope so that the subject, study site or sponsor stay masked to the treatment until the end of the study. The investigator should not reveal the nature of the treatment to the subject, study site or sponsor until after the end of the study.

Unintentional unmasking: In case of unintentional unmasking by the subject or clinical staff, the date and reason must be documented in a source document and the sponsor shall be informed immediately. The sponsor will decide whether the subject should be kept in the trial, re-randomized, or withdrawn.

1.9.8 Dose Abuse, Lost Medication or medication shortage

1.9.8.1 Dose abuse

Subjects will be highly discouraged to take more than one capsule per day, except in the case of a missed dose. Because only the percentage of deuterated vitamin A, rather than the absolute values of vitamin A affects efficacy, there is no expected benefit in taking more than one capsule per day. Instead, taking more than one dose per day may lead to adverse reactions and subject withdrawal from the trial for non-compliance with the study instructions.

1.9.8.2 Lost medication or medication shortage

In the event a subject loses one medication bottle, a replacement bottle will be provided if available. To avoid abuse, subject will be informed that they could be withdrawn from the study if they lose their medication bottle a 2nd time. Second replacement bottles can be provided only at the discretion of the sponsor and only under exceptional circumstances. No more than two replacement bottles will be provided.

If for any reason the subject's study drug supply ends up being insufficient to complete the study, subject should be scheduled for the 24-month follow-up visit within minus 1 (-1) and 8 days of running out of study drug supply, preferably when the subject still has at least 1 remaining capsule of study drug ("1 day before running out"). If this follow-up visit ends up outside of the visit window, it should be documented as a protocol deviation.

1.9.8.3 Lapse in treatment

If a lapse in treatment occurs during the treatment period for any reason, the days and duration that the subject was off-treatment shall be documented. If the subject is off-treatment for a period longer than 4 weeks in a relatively continuous manner, and if the subject lives relatively close to the study site, the study team may collect the subject's plasma in an unscheduled visit to acquire data on the study drug pharmacokinetics due to the lapse in treatment.

Lapse in treatment may occur for a variety of reason, including health-related reason, temporary discontinuation, lost medication, subject forgetting to take treatment, study drug availability, family or personal reason, etc.

Lapse in treatment shall not result in modifications of the visit windows, unless agreed upon by study staff and sponsor. Lapse in treatment may also result in early withdrawal.

1.9.9 Study Drug Physical Description

The study drug unit dosage is an opaque hard gelatin capsule. All capsules containing active ALK-001 or placebo look, weigh and smell the same and cannot be differentiated. Capsules are packaged and sealed in opaque white plastic (HDPE) bottles with a child-resistant cap. Bottles may contain an oxygen scavenger pouch (or canister) and a cotton ball. Both cotton ball (and any residual cotton threads) and oxygen scavenger should be taken out of the bottle after breaking the seal and must be discarded. The oxygen scavenger is not needed once the seal has been broken.

Real-time stability data will be acquired throughout the study to ensure stability of all dispensed medications. Based on existing stability data acquired on the previous batches of study drug,

capsules should be stable for at least 24 months. Bottles deemed to contain capsules out of specification may be collected by the sponsor and replaced by new bottles.

1.9.10 Packaging and Labeling

Each bottle delivered to the sites will have a label already affixed to it. A sample of the label is found in section 1.22.1 and includes the following statement: "**CAUTION – NEW DRUG : LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE**.". The label contains a medication ID # corresponding to the randomization code (eg: CA27), and dosage instructions for the study subject.

1.9.11 Testing, Tampering Study Drug Prohibited

It is prohibited to tamper with the study drug, including used medication bottles and contents collected from subjects. Any unused study drug is the sole property of the sponsor and shall not be broken down, analyzed, or tested in any way. Returned medications shall be stored at the site until its destruction (if requested by the sponsor), collection by or shipping to the sponsor.

1.9.12 Study Drug Supply: Receipt, Storage, Dispensing and Disposal/Return

1.9.12.1 Receipt of Drug Supplies

Sponsor will be responsible for coordinating the shipment of study drug to the sites or to the study subjects.

Upon receipt of any study drug, an inventory must be performed by the study staff and a drug receipt log be filled out. Any damaged or unusable study drug in a given shipment shall be documented and immediately communicated to the sponsor.

1.9.12.2 Study Drug Storage

General storage and temperature monitoring: All study drug should be stored at room temperature, unless instructed otherwise in directions accompanying the study drug. Temperature should be monitored and recorded at least once daily with an appropriate device.

All study drug should be stored in a locked room or cabinet, and everyone with direct access should be disclosed in the regulatory binder. Such room might be the pharmacy, research pharmacy or the investigator's office, so long as the study drug is stored in a locked cabinet/safe separate from FDA-approved medications, and the temperature is appropriately monitored. Because the product is light sensitive, the storage environment should not expose the study drug packaging to constant light or to direct sunlight. Study drug can be stored next to other investigational drugs.

Storage of returned/collected study drug: Returned, used or unused study drug should not be stored together with the study medication (unless permission is provided by sponsor) and do not need to be stored in a locked environment.

1.9.12.3 Dispensing of Study Drug; Direct to Patient Shipment

Dispensing by designated personnel only: For study drugs stored at the study site, study drug shall be dispensed only by designated personnel.

Two signatures required: To ensure that the proper medication ID is dispensed, dispensing shall be performed by one designated person plus another person assisting and checking that the proper medication is being dispensed. Exceptions may be granted by sponsor in case of scheduling or other challenges.

First dispensing: When a subject receives the study medication for the first time, instructions should be provided to the subject regarding storage conditions (room temperature, do not store in a car or in a sunny area), how to open the bottle, and at what time to take the study drug (same time as other medications). Subject should break the seal, discard the cotton ball if present (and any possible residual cotton threads), and discard the oxygen scavenger if present, which is not useful once the seal has been broken. The first capsule should be taken in front of the person dispensing the medication, and the subject observed for approximately one hour prior to being discharged.

Direct to patient shipping by site, research pharmacy or sponsor representative: study drug may be shipped directly to the subject by the study staff, research pharmacy or by a sponsor representative. Study drug shall be packaged in standard unmarked cardboard boxes. Unless unavailable or impractical, which should be documented, shipping to patient must be overnight with delivery before 10am and direct signature required. All study drug shipment shall be adequately logged.

Exposure of study staff to study drug*:* ALK-001 is a vitamin A. Vitamin A is mildly teratogenic and is not considered a hazardous drug. No special precautions beyond reasonable care are required for the handling of the study medication. The study drug is formulated in an oil, self-contained in individual and sealed unit-dose capsules, packaged in a sealed plastic bottle, the content of which will only be accessed by the study subject. As such there is very little risk of environmental exposure of the study staff to the study drug.

1.9.12.4 Return/Disposal of Study Drug

Return of medication bottles by subjects: Subjects should be instructed to return all used or empty, partially used, or unused bottles to the study site at each visit. Remaining number of capsules should be recorded at time of return. Remaining capsules may be transferred into a freshly dispensed bottle of study medication unless directed otherwise by sponsor.

If a subject has to permanently discontinue taking the study drug, all study drug material shall be collected from the subject. Such collected medications should not be administered to any other subject, nor used for any purpose besides storage at the site.

Storage and destruction of collected study drug. The site staff will retain all such collected material until the study monitor has performed drug accountability. Collected medication bottles should be stored separate from the unused bottles (except when permitted by sponsor), and if such medication bottles still contain unused drug, in a locked cabinet/safe/drawer accessible by designated personnel only. The sponsor or monitor will pick-up these bottles, or they will be shipped to sponsor or to a designated facility for destruction, or destruction at the site will be requested, if feasible. No destruction should take place without the written request from sponsor.

At trial completion, site close-out, or upon request by sponsor, unused study medication may be returned to sponsor or shipped to a designated address. Bottles will be shipped using standard

couriers such as UPS, USPS or Fedex. If necessary, sponsor will provide a temperature logger and specialized shipping containers and instructions.

1.9.13 Drug Accountability

1.9.13.1 Drug supply

The study staff will maintain records of study drug delivery to the site, study drug inventory, the amount of bottles of study drug provided to each subject, the amount of unused study drug returned to the site by the subject, the amount of unused study drug returned to the sponsor (or where otherwise mandated, a certificate of destruction of any unused study drug). Study monitors will verify the site's study drug and accountability records.

1.9.13.2 Subject drug reconciliation

At each follow-up visit, the study staff will count all remaining capsules in each subject's bottles, and calculate the theoretical numbers of remaining capsules. Data will be recorded in the source document and any significant discrepancy investigated.

Non-compliance may result in withdrawal of the subject and must be thoroughly investigated by the investigator and clinical team.

1.10 MONITORING OF COMPLIANCE

Compliance will be assessed and encouraged using the following means:

- *At each visit:*
    - Study staff should discuss the importance of treatment compliance with subjects (daily drug intake, timing of drug intake, avoidance of vitamin A containing supplements, avoidance of vitamin A-rich items, and avoidance of other types of supplements except when permitted).
    - Study staff should perform study drug reconciliation by counting the number of capsules remaining in the dispensed bottles and comparing this number to the theoretical number of capsules remaining.
    - Study staff should remind subjects that they may be withdrawn from the trial at any time if they are thought to be insufficiently compliant.
- *Between visits:*
    - Clinical staff will call subjects periodically to check compliance with the study drug and study instructions. This phone call should be made at least once a month. Documented evidence and written notes detailing the content of each phone call should be taken.

1.11 PRIOR AND CONCOMITANT MEDICATIONS; RESTRICTED FOODS AND MEDICATIONS

1.11.1 Prior (pre-treatment) and Concomitant Therapy

1.11.1.1 Prior medication or therapy (before randomization/treatment)

The investigator should record as prior medication or therapy all medications, including prescription and over-the-counter medications, vaccines, vitamins and supplements, taken by the subject from 30 days prior to the start of screening, up to the day of randomization. Investigator should also record retinoid therapies taken up to 6 months prior to screening. This includes any vitamin A-containing supplements, accutane, acitretin, retinoic acid, bexarotene, etretinate.

Preexisting clinically-effective therapies for a subject's existing condition must not be changed for the purpose of satisfying eligibility requirements and entering the subject into the study.

1.11.1.2 Concomitant medications and/or therapy (during treatment)

Starting from the administration of the first dose of the study drug, investigator shall record all concomitant therapies. These include prescriptions or over-the-counter medications, vaccines, vitamins, and supplements.

Efforts should be made to keep subjects' concomitant therapies stable throughout the study. Any change and reason for change in concomitant therapies should be documented.

1.11.2 Restricted Foods and Supplements

1.11.2.1 Vitamin A from liver and Vitamin A Supplements

All study participants should be advised that taking vitamin A from food will reduce the activity of the drug.

1.11.2.1.1 Prohibited

Specifically, subjects will be informed to **not** consume:

- Food items that contain excessively large amounts of vitamin A. These include: **liver-based products** (including liver oil, liver sausage, foie gras, etc.), giblets
- **Vitamin A or beta-carotene containing supplements**.

At screening, the investigator should check whether the prospective subject has used vitamin A or beta-carotene containing supplements over the past 30 days. If so, prospective subjects must stop and not take any vitamin A and beta-carotene containing supplements, at any dose, at any time during the study.

1.11.2.1.2 Allowed

Food items that contain moderate amounts of vitamin A are allowed with moderation (i.e. a maximum of approximately 3 servings per day). These food items include: fortified cereals, dairy products (yogurts, creams, milk, eggs, butter), some processed foods.

Subjects will be educated on how to identify vitamin A content from nutrition facts label, and be

informed that most vitamin A fortified food items, such as cereals, yogurt, or processed food, nearly always have multiple choices of non vitamin A-containing alternatives (including from the same brand). Subjects will be encouraged to seek those alternatives by reading the food labels. Please provide instructions from section 1.22.2 (as updated and IRB-approved) to every subject.

Fruits and vegetables are allowed without any restrictions. They only contain carotenoids which are poorly absorbed and converted to vitamin A when taking preformed vitamin A.

1.11.2.2 Recommended: AREDS-2 or Equivalent. Prohibited: AREDS-1

At screening, the investigator should investigate the use of AREDS and AREDS-2 supplements.

AREDS is prohibited: AREDS contain beta-carotene, which is disallowed during the study. Subjects who are taking AREDS at screening should immediately stop taking AREDS until the end of the study.

AREDS-2 is recommended: AREDS-2 has shown that it could slow the progression of intermediate to advanced AMD by 25%. In this study, AREDS-2 is recommended for all patients, especially those with intermediate AMD in the fellow eye. Subjects who decide that they want to start taking AREDS-2 will be instructed to start taking it immediately. This is to avoid adding new concomitant medications during the study.

1.11.2.3 Prohibited: Other Supplements

At screening, the investigator should investigate the subject's use of supplements. To avoid confounding effects, supplements containing ingredients such as saffron, curcumin (turmeric), bilberry, fish oil, DHA, EHA, lutein, zeaxanthin, omega-3-fatty acids, resveratrol, CBD oil, and "multivitamins for vision" (except AREDS-2), will be prohibited from screening until the end of the study. When in doubt, all multivitamin formulations, except AREDS-2 should be discontinued for the duration of the study.

1.11.2.4 Prohibited: Over two (2) alcoholic beverages a day

Because alcohol consumption can result in accelerated metabolism of vitamin A and secretion by the liver, increasing the risk of adverse reactions [97], subjects will be encouraged to limit their alcohol consumption to two (2) alcoholic beverages a day.

1.11.3 Concomitant Medications, Prohibited and Restricted Medications, Participation in Other Clinical Trials

Prohibited retinoid therapies: Throughout the study, subjects should be prohibited to take any retinoid-based medication (including acutane, isotretinoin, acitretin, retinoic acid, bexarotene, etretinate) except in the case of a medical necessity. Retinoids may trigger significant ocular and systemic adverse reactions, and could interfere with the pharmacokinetics or the mechanism of action of ALK-001.

Restricted medications: antibiotics of the class of tetracycline are known to interact with vitamin A. As such, tetracyclines should not be used by the subject unless no other class of antibiotics

would be deemed efficacious in the subject. Tetracyclines include for example Demeclocycline (Declomycin), Minocycline (Minocin), Tetracycline (Achromycin).

Prohibited prescription eyedrops: Unless medically necessary, subjects are prohibited to use eyedrops except for over-the-counter lubricating eyedrops, for which there are no restrictions. When medically-necessary however, FDA-approved prescription eyedrops may be used according to the approved label (no off-label use). Exception can be granted by the investigator and sponsor, for medical reasons, which should be documented.

Prohibited participation in other trials or studies: subjects should be prohibited to enroll or participate in any other clinical trials that involve a drug or treatment (investigational or not) for the treatment of GA, AMD or for any other condition, unless clinically necessary and recommended by the PI and approved by sponsor. Subjects are also prohibited to enroll in studies that involve retinal imaging (see section 1.12.34.1).

Medication/Food/Drinks	**During Treatment**
Liver, liver oil, sausage, foie gras, giblets	Prohibited
Vitamin A-enriched food products (cereals, yogurts, creams, milk, eggs, butter)	Under ~3 servings/day
Fruits & Vegetables	No restriction
Vitamin A or Carotene containing supplements	Prohibited
AREDS and AREDS-2 supplements	AREDS: prohibited AREDS-2: encouraged
Following supplements: saffron, curcumin (turmeric), bilberry, fish oil, DHA, EHA, lutein, zeaxanthin, "multivitamins for vision", omega 3 fatty acids, resveratrol, CBD oil	Prohibited
Following medications: acutane, isotretinoin, acitretin, retinoic acid, bexarotene, etretinate	Prohibited
Prescription eyedrops, except when medically necessary and according to FDA approved use	Prohibited
Tetracycline antibiotics	Only if no other antibiotics class is available
Alcohol beverages	2 drinks max. per day

1.12 ASSESSMENTS AND ORDER OF PROCEDURES

Table of all events, timing and schedule is found in section 1.2. Details for each procedure is provided in this section, with practical details in the manuals of operation.

1.12.1 Primary Study Eye

The PI and sponsor should agree on the choice of primary study eye by evaluating all inclusion criteria for each eye. The primary study eye must be chosen prior to running any analyses on atrophic lesions. The following guidelines, which may be amended from time to time in the manual of operations or the source documents should be used to choose the study eye:

- For subjects with only one eye with geographic atrophy that meets all "study eye" inclusion criteria, that eye should be selected as the primary study eye.
- For subjects with both eyes that meet all inclusion criteria, the following criteria will be prioritize to decide on the study eye:
    - Well-delineated and accurately measurable atrophic lesions
    - Atrophic lesions likely to stay within the field of view over the next 2 years
    - Atrophic lesion border is closest to foveal center (in the case of foveal sparing)
    - Visual acuity is closest to the range 20/40 to 20/100.
    - Imaging availability and quality at all time points during the study

During the study, both eyes should undergo all procedures, or as described in the manual of operations. Prior to the performance of unmasked statistical analyses, and based on the totality of data available at that time of analysis, the investigator and sponsor may choose a different study eye, which shall be documented.

1.12.2 Order of procedures

Order of procedures will be provided in the manual of operations, which may be amended from time to time. General guidelines are provided here:

1. **Non-ocular subject examinations: 12-lead ECG** and **physical exam can be performed** at any time, except that 12-lead-ECG may be performed *preferably* upon the subject's arrival and before blood draw.
2. **Blood draw** should preferably be performed first upon the subject's arrival, especially since the patient is likely to be fasting. While blood samples and plasma are being processed, subject may be asked to fill out the patient-reported questionnaires.
3. **Patient-reported questionnaires** and other **patient reported outcomes (PRO)** should preferably be conducted first upon the subject's arrival, before the subject has been dilated.
4. **Study drug intake**: During follow-up visits and assuming the subject is used to taking the study drug in the morning, the subject may then take his/her daily study-drug and have a snack after blood samples have been collected.
5. **Undilated ocular tests** should preferably be performed in the following order:
    - **ETDRS-BCVA** (preferably using standard ETDRS charts or the EVA system)
    - **Reading speed**
    - **Low luminance visual acuity**
6. **Dilated ocular tests** should preferably be performed in the following order:
    - **IOP**
    - **Keratometry**, wherever available should be performed once during the study to acquire ocular parameters

- **Microperimetry**, wherever available, except that at screening, OCT may be performed before microperimetry, in order to locate the anatomical fovea, required for placement of the microperimetry testing grid. Because microperimetry is sensitive to light or dark adaptation status, microperimetry must never be performed following fundus autofluorescence, dark adaptation, or electroretinograms. However, if there is no other choice due to site logistics, at least one hour should lapse after performing fundus autofluorescence, dark adaptation, or electroretinography before performing microperimetry.
- **SD-OCT**
- **Fundus autofluorescence (FAF)**
- **Fluorescein angiography or OCT angiography (according to site or PI standard of care)**
- **Color Photo (optional)**
- **Dilated ocular exam or assessment:** biomicroscopy, fundus exam, according to PI standard of care

Screening visit (V01) should preferably start early in the morning to allow sufficient time to complete all screening activities in a day. However, to reduce subject fatigue, for scheduling or planning purposes, or for any other reason, study staff may choose to complete the screening assessments over a period of multiple days, which is allowed for as long as all screening activities are completed within 40 days from the first day of screening. In this case, all screening activities all screening activities shall be recorded on the screening "V01" source document template, but shall indicate the date actual performance of the procedure/assessment.

The following sections provide details about each procedure/assessment in the order they appear in the table of section 1.2.

1.12.3 Informed Consent

Before any study-related assessment is performed, the study staff must go through an informed consent process with each prospective subject. At the end of the informed consent process, the subject must sign and date a study-specific, IRB-approved, informed consent form (ICF). See 1.19.3 for more details.

1.12.4 Demographics

General demographic information will be collected, which shall include for example: date of birth, age, gender, ethnicity, race, age of onset of GA, age of onset of AMD, highest education, current or previous occupation if retired, smoking and driving status.

1.12.5 Size 0 Capsule Swallow Test (Optional)

Subjects enrolled in the trial should be capable of swallowing a size 0 capsule, which is approximately similar in size to AREDS-2 softgels, and smaller than most multi-vitamin tablets. During the screening visit, the study staff should inquire whether the subject has already taken size 0 capsules. If in doubt, investigator may provide the prospective subject with an empty or placebo-filled size 0 capsule, if available, to verify that subject is able to swallow such capsule.

1.12.6 Clinical Diagnosis

Subjects should be confirmed to have been diagnosed with geographic atrophy secondary to age-related macular degeneration.

1.12.7 Medical, Surgical and Ocular History

1.12.7.1 General medical history

Systemic medical history will be elicited from all subjects during screening, and is key to establish an adequate baseline of the subject's pre-existing medical history, condition, and symptoms. Medical history shall include a complete review of systems, past medical and surgical histories, and allergies. Medical history will then be used to assess any disqualifying medical conditions.

In particular, check for:

- History of poor intestinal absorption that could result from celiac disease, crohn's disease, small-bowel resection, pancreatic insufficiency, intestinal bacterial infection
- History of prior gastrointestinal surgery except appendectomy, hernia repair or cholecystectomy
- Poor mental development or impaired cerebral function
- History of alcohol dependence or abuse
- History of liver disease, cirrhosis or poor liver function as measured on laboratory assays
- History of neurologic or neuromuscular disease
- History of hypotension or cardiovascular disease
- History of diabetes, chronic hyperlipidemia, hepatitis, pancreatitis
- History of ocular disorder that may confound assessment of the retina, such as cataract surgery within the past 6 months, CNV, glaucoma, recurring uveitis, diabetic retinopathy, other retinal diseases, etc.
- History of any condition that might interfere with the study treatment, might prevent execution of the study procedures, or might impair the ability of the subject to participate in the study for 24 months.

1.12.7.2 Ocular history and collection of historical retinal images

Thorough ocular history shall be collected from the subject, and all historical results, reports, data, photographs shall be included in the subject binder, and might be used in retrospective analyses. Ocular medical history shall contain:

- any use of eye-related medication, including off-label and supplements
- previous or current participation in any clinical trial
- any other relevant ocular disorder or surgery (see general medical history above)
- age of onset of geographic atrophy
- age of onset of AMD
- quality of life/visual function questionnaires (self-administered)
- results of historical tests should be sought and requested from the subject. If necessary, subjects should provide permission to their previous healthcare professional to disclose these results to the clinical site. Data most important to gather are the following:
    - all genetic test report(s)
    - all fundus autofluorescence imaging

- all microperimetry testing results
- all color fundus photos
- all OCT photos

All results shall be included in the subject binder and may be used in retrospective analyses.

1.12.8 Vitamin A Information, Counseling & Quiz

Throughout the study, subjects should be reminded to avoid any vitamin A or carotene containing supplements, as well as all food items containing high levels of vitamin A (see section 1.11.2 for details) as this would interfere with the study drug and reduce its activity.

At screening, printed instructions on how to reduce vitamin A intake will be provided to subjects (section 1.22.2). A self-administered paper quiz may be provided to the subjects to ensure that they understand the instructions. Results of this quiz are not used to determine the subject's eligibility but rather to help the patient assess their understanding of nutritional vitamin A intake.

1.12.9 Eligibility (Inclusion/Exclusion) Criteria

All enrollment criteria will be reviewed between the Screening (V1) and the Randomization (V2) visits before randomization can be performed. All Screening assessments may be completed up to the day of randomization.

1.12.10 Prior and Concomitant Medications

See section 1.11.

1.12.11 Adverse Events and Serious Adverse Events (SAEs)

At each visit, adverse events (AEs) should be carefully discussed with the investigator and study staff. AE reported by the subject, or when appropriate caregiver or the subject's legally acceptable representative, shall be timely recorded in an AE log. All reported AEs should be carefully followed by the study staff. See section 1.16.1 for details on AE and SAE recording and reporting.

1.12.12 Check-up phone call / Short visits replaced by phone calls or visiting nurses

Phone check-up: Following randomization, the clinical staff should call subjects periodically. In particular, check-up phone calls should be made:

- on the day after the first dose,
- at least monthly thereafter

The frequency of the check-up calls may be increased based on specific subject's needs, health and/or compliance risk as judged by the sponsor or the investigator. During these phone calls, the site staff will inquire about the subject's general health and any adverse events, concomitant medications, and to ensure compliance with the study treatment and with the restriction of items containing high amounts of vitamin A (no liver products, no vitamin A/beta carotene containing supplements).

The site staff should also call subjects to remind them of their upcoming visit and of the need to come fasting (preferably) for the visit (including no study drug the morning of the visit).

Phone calls should be documented in an appropriate log.

Short visits may replaced by phone calls or in-person visiting nurse*:* The visit schedule may be challenging especially for visually-impaired, elderly subjects who may live far from the study site. As such and to reduce the visit burden, and only upon sponsor's approval, the study staff may be allowed to replace in-person visits V03, V05, V07, and V09, by phone check-up (as described above), or by in-person visits to the subject's residence by a home nurse or equivalent, as delegated by the PI. This should only be allowed if the subject does not have any continuing AE related or possibly related to the study drug, and if the subject is known to be compliant with the study requirements.

Sponsor and PI shall prioritize safety in making their decision.

1.12.13 Study Drug Reconciliation

See section 1.9.13.2

1.12.14 Vital signs

Weight (shoes off preferably) measured or converted in pounds (lbs), **height** (shoes off preferably) measured or converted in inches (in), and **body temperature** (preferably oral, measured or converted in Farenheit °F) should be acquired. After the subject has been able to rest seated for approximately 5 minutes, **respiratory rate** (RR in breaths per minute), **heart rate** (HR in beats per minute) and **blood pressure** (BP in mmHg) should be measured. Blood pressure should be taken seated, with supported back, both feet flat on the floor, after the subject has been sitting for at least 5 minutes. Preferably, the left arm should be used. The same arm should be used at each follow-up visit whenever possible.

1.12.15 12-lead ECG

Vitamin A is not known to affect the ECG. ECG is performed in this study to exclude patients who may have clinically-significant abnormal ECG. During the study, ECG is used to monitor that there are no clinically-significant abnormalities.

A standard 12-lead resting ECG should be taken supine, if possible before any blood is collected. Prior to taking the ECG, the subject shall lie down and rest in a quiet setting without distraction (no cell phone, no television) for at least 5 minutes. During ECG recording, the subject should not talk or move arms or legs. All recorded ECG traces must be printed out. No name shall appear on the ECG printout. Instead, use the subject ID, initials, date of birth and gender. The same ECG equipment should be used throughout the study if possible. Unscheduled ECGs may be performed if clinically-indicated by the PI.

ECGs are frequently interpreted as "abnormal" by the ECG machine internal algorithm even for healthy subjects. If the ECG is interpreted as abnormal or if the QTc is greater than 460 msec for male or 480 msec for female, approximately at screening), the person acquiring the ECG should verify all electrode placements and proper attachments, let the subject rest for another 5 minutes and record and print a second ECG trace. Both ECG traces should be printed out then interpreted

by the PI or designated personnel. Special care should be taken during electrode placement, including skin preparation (shave extra hair, gently rub the skin to remove the dead skin layer).

In all cases, the PI or person interpreting the ECG should sign the ECG printout(s) (email acceptable if it contains all personal information about the subject), indicate which QTc to use (or manually calculate the average of QTc values if more than one ECG printouts are available), and conclude whether the ECG is normal or abnormal. If abnormal, the investigator should mention if the abnormality is "non-clinically significant" (NCS) or "clinically significant" (CS). If the ECG is abnormal, comments should be also added. All printouts need to be scanned and archived.

To prevent enrolling subjects with pre-existing heart conditions, subjects with QTc greater than approximately 460 msec for male and 480 msec for female, at screening should not be enrolled in the study unless otherwise authorized by the sponsor. During treatment, subjects with an average QTc higher than 500 ms based on duplicate ECGs should be discontinued from treatment, unless decided otherwise by PI and sponsor.

1.12.16 Physical exam or Assessment

Physical exam shall be performed by the PI or other medically licensed personnel authorized to perform physical examinations in the country or state of the site. Physical assessment may be performed by registered nurses in case some of the optional visits are performed at the subject's residence.

If possible, all physical examinations for an individual subject should be performed by the same personnel at each visit. The physical exam can be comprehensive (C) or simplified (S) (see table of section 1.2 for exact schedule)

- *Comprehensive physical exams* includes most body systems: general appearance, skin, eyes, ENT, head neck & thyroid, heart, lungs, chest, abdomen, extremities, lymph nodes, musculoskeletal, neurological, except genitalia, anorectal and breast exam, which are optional.
- *Simplified physical exam* includes general appearance, skin, eyes, ENT, head neck & thyroid, heart, lungs, abdomen, musculoskeletal.

Clinically-significant findings observed after the subject has started treatment, and which are not deemed to be a preexisting condition (see 1.16.1.2), should be reported as AEs.

1.12.17 Eye exam (both eyes)

Eye exam should be performed by the PI or medically-licensed personnel on both eyes, according to standard of care practices, and include:

- keratometry (if available at the site, for measurement of corneal curvature),
- intraocular pressure (IOP),
- pupillary exam (unless the patient is already dilated at the time of exam),
- slit lamp exam,
- dilated fundoscopic exam.

1.12.18 Visual Acuity ETDRS BCVA (both eyes)

Best-Corrected Visual acuity of both eyes should be acquired according to the manual of operations. Although preference is to use standard ETDRS charts for refraction and measurement of BCVA, digital charts or computer-based systems (such as "EVA") are acceptable. The same chart/system (ETDRS, EVA or other) must then be used at all follow-up visits.

1.12.19 Low Luminance Visual Acuity (both eyes)

Low luminance visual acuity should be acquired according to the manual of operations, using the same refraction and trial lenses used for BCVA.

1.12.20 Reading Speed Test

Reading speed tests shall be performed according to the manual of operations, with the subject wearing the same refraction and trial lenses used for BCVA.

The MNREAD and the International Reading Speed Test (IReST) [98] (and/or equivalent) will be used. For IReST, English texts will be used, except if the subject strongly prefers a different language or does not speak English. The same language should be used at each visit and sponsor will indicate which text to use for which visit.

1.12.21 Vision Questionnaire & Survey

Subject shall complete the following vision questionnaires according to the manual of operations:

- The visual function test VF-14 (section 1.22.3),
- Functional Reading Independence (FRI) index (sample in section 1.22.4) licensed from Genentech,
- Macular Disease Dependent Quality of Life (MacDQOL) (licensed from Health Psychology Research)

Questionnaires that are filled out directly by the subject should be IRB-approved. The choice of visual function tests may be amended from time to time by the sponsor.

1.12.22 Color Fundus Photograph (CFP)

CFP is optional and may be acquired according to standard of care practices.

1.12.23 OCT Angiography (OCTA) or Fluorescein Angiogram (FA)

PI shall follow standard of care practices to diagnose CNV, using either OCTA or FA

1.12.24 Fundus Autofluorescence FAF (both eyes)

FAF images should be acquired according to the manual of operations. FAF images acquired during the screening period must be promptly shared with the sponsor or reading center to verify subject eligibility.

1.12.25 Spectral Domain-OCT (both eyes)

SD-OCT images should be acquired according to the manual of operations.

Important: OCT scans taken during the screening visit shall be immediately set as "reference", even in the absence of follow-up and before transfer to the sponsor or reading center, so that follow-up images can be compared to initial scans. For follow-up visits, make sure the "follow-up" tool has used, and that the proper reference scans taken at screening are selected.

1.12.26 Treatment of CNV

PI shall follow standard of care practices to decide whether to treat any patient who presents with CNV seen on FA or OCTA.

1.12.27 Microperimetry (both eyes, where available)

Microperimetry should be acquired according to the manual of operations, where microperimetry is available. Follow-up testing should use the "follow-up" function to ensure that the same anatomical points are tested and can be compared to previous values.

1.12.28 Clinical Laboratory

Blood samples for chemistry, hematology, lipids, pregnancy (if performed), complement, genetic, and drug PK (or related substances) will be collected according to the schedule of assessment. During repeat or unscheduled visits, blood samples may also be collected to test the below analytes or because of technical issues with the samples.

When blood is collected, the subject should preferably have been fasting for 8 hours, although subjects who need to eat will be allowed to eat fruits, and drink water prior to blood sample collection. The duration the subject has been fasting should be recorded on the source document. The number of hours elapsed since last study drug intake should also be recorded. Blood samples should be handled according to a lab manual, labeled, then forwarded to either the central laboratory or the institution's designated laboratory for testing.

The PI must review all clinical laboratory reports and document this review by dating and signing off on the report, marking any abnormal value as clinically significant (CS) or non-clinically significant (NCS). Clinically-significant abnormalities measured after start of treatment should be recorded as AE (see section 1.15.7.2 for details).

Sufficient blood should be drawn to perform the following tests:

- Lipids:
  - Total cholesterol,
  - HDL,
  - LDL,
  - Triglycerides.
- Biochemistry:
  - Sodium,
  - Potassium,
  - Chloride,
  - Bicarbonate,
  - Urea,
  - Creatinine,
  - Calcium,

  - Total Protein,
  - Bilirubin,
  - Albumin,
  - Alkaline phosphatase (Alk Phos),
  - AST,
  - ALT.
- Hematology:
  - Hemoglobin (HGB),
  - Hematocrit (HCT),
  - Mean corpuscular volume (MCV),
  - Mean corpuscular hemoglobin (MCH),
  - Platelets (PLT),
  - Red blood cell (RBC) count,
  - White blood cell (WBC) count,
  - Neutrophils (absolute and percent),
  - Lymphocytes (absolute and percent),
  - Monocytes (absolute and percent),
  - Eosinophils (absolute and percent),
  - Basophils (absolute and percent).
- Glucose:
  - HbA1c

Additional laboratory tests may be performed upon request by the sponsor, or as clinically indicated by the PI, but only after approval by the sponsor.

1.12.29 Vitamin A and Pharmacokinetics (PK)

Collection and processing of blood/plasma sample. The number of hours since the last study drug intake should be inquired and recorded. About 6 to 8 mL of blood will be collected in a K2-EDTA (purple top) tube. The tube will be pre-labeled and immediately covered with foil and placed in an ice bath if not immediately processed. The sample should be spun down for 10 minutes at 3,000-3,400 rpm, and plasma should then be transferred into 2 provided amber glass vials (one used as back-up in case of loss/damage), covered with foil, and immediately frozen.

At least 1 mL of plasma is required for proper testing. Because one (1) mL of plasma is necessary for proper testing of the plasma samples, the study staff should ensure that at least one vial contains 1 mL of plasma.

Store frozen. Plasma samples should be stored frozen at approximately or below -20°C and preferably below -70°C for storage longer than 3 months, a duration which may be modified from time to time by the sponsor.

Ship upon request. Periodically, the sponsor or representative will request the study staff to ship available plasma samples to the bioanalytical lab, where a validated assay will determine the concentrations of various metabolites of ALK-001 and their corresponding non-deuterated vitamin A metabolites.

Lab manual to provide detailed instructions about the supplies, collection, handling and shipment.

1.12.30 Complement and Genotype

Blood samples will be collected according to the manual of operations, to measure complement activity and the subject's genotype. Please refer to section 1.7.2.10 for details.

1.12.31 Pregnancy Test, Contraception Requirements

Female subjects of childbearing potential will not be allowed to enroll in this study. Nonetheless, PI may request a pregnancy test during the screening period.

During the study, there are no specific contraception requirements for subjects enrolled in the study. Nonetheless, if a male subject's female partner becomes pregnant during the treatment period, the pregnancy must be reported to the sponsor within 24 hours of the site's knowledge of the pregnancy. Information on the pregnancy will be sought by the investigator until the end of the pregnancy (i.e. normal delivery, still birth, miscarriage).

1.12.32 Compliance (dietary and drug)

See section 1.10 for details.

1.12.33 Drug dispensing

See section 1.9.12.3

1.12.34 Other Procedures

1.12.34.1 Unscheduled procedures/assessments prohibited

Subjects will be informed that they must not undergo any other ocular tests, exams or procedures, performed by any other optometrist or ophthalmologist who is not an investigator in the study, until the end of the study.

Except in case of a technical issue (eg: blood draw) or insufficient quality (eg: imaging), or in the case of medical emergency or necessity which should be documented, the investigator must not perform, allow, or request performance, of any procedure, ocular or blood, imaging, electrophysiological, psychophysical or any other test procedure or assessment that is not scheduled on the events table of section 1.2, unless authorized by sponsor, so as to preserve the integrity or quality of the data.

1.12.34.2 24-hr PK testing authorized upon request by the sponsor

Because it is unrealistic to perform a long-term pharmacokinetic study in healthy volunteers, detailed pharmacokinetic data of subjects who have been receiving ALK-001 for several months may be more readily acquired by including subjects participating in this study. For that, the investigator, SMC or sponsor might request that some subjects stay at the clinical site for a 24-hour overnight stay. Shorter than 24-hour stays may be admissible and should be agreed upon by the sponsor and the investigator on a case by case basis. Subjects should be informed with reasonable advance notice and should have the choice to accept or refuse to participate, which

shall not affect their participation in this study. In case they accept, **the subject will sign a separate informed consent, which shall be IRB-approved**.

For each subject, blood samples should be collected at regular intervals (suggested: 2 and 4 hours post dosing, then every 4 hours for a total of 24 hours post dosing) and processed as described in the bioanalytical manual. In the case of an overnight stay and to reduce the burden on the clinical site, the subject might stay in another designated clinical site (such as a phase 1 unit for example) to perform such pharmacokinetic study.

To avoid unmasking, at least 3 subjects will be asked to participate in this PK sub-study, one in the placebo group, and two in the ALK-001 group.

1.12.34.3 End of treatment period: optional open-label extension period

Following completion of the initial treatment period of 2 years, subject may be given the choice to enter into a two-year open-label extension study. In order to enroll in this study, the subject will sign a separate informed consent, which shall be IRB-approved. Subjects who elect not to participate in the optional open-label study will be considered to have completed the study.

This optional study will assess the long-term pharmacokinetics of various dose levels of ALK-001, in order to estimate the smallest daily dose level that can maintain approximately 80% of deuterated vitamin A in plasma. In addition, fundus autofluorescence imaging will continue to be acquired and efficacy analyses on the growth rate of geographic atrophy will be performed on all subjects. This study will follow most standard of care practices. **Further details will be provided in future protocol amendments.**

1.13 SCREENING VISIT AND RANDOMIZATION VISIT: DETAILS

1.13.1 Screening Activities (approximately 20 to 40 days prior to randomization)

All screening activities ("V01") should be completed between 20 and 40 days prior to randomization ("V02" = day of 1st dose administration of the study drug). To avoid screen failures, investigators should use their best judgment and only screen subjects they believe will meet all eligibility criteria.

Run-in period to measure compliance during screening: Because the study lasts for 2 years, it is important to get a sense of the subject's compliance before randomizing the subject. Therefore, at the beginning of the screening activities, investigators may offer the subject a bottle of placebo-containing capsules to assess compliance during the screening period. At V02 and before randomization, compliance would be deemed sufficient if it is greater than approximately 80%. If this is the case, the subject may be randomized and continue the study. If not, the PI may decide to further discuss with the patient or to withdraw the patient from the study.

Screening: After a comprehensive description of the protocol, review of ICF, and all questions have been answered, subject will have the opportunity to decide if they want to participate in the

study and sign the ICF. The informed consent must be obtained prior to perform any study-related procedures (See section 1.19.3 for details).
After obtaining consent, each subject will be assigned a unique screening ID number. This number will be provided by the sponsor upon request by the site. The sponsor will inform each site of the subject ID format.

Subjects are then interviewed to determine their preliminary eligibility for enrollment by assessment of inclusion and exclusion criteria. If a subject meets these criteria, all procedures listed in Section 1.2 are performed. Investigator is encouraged to send the screened subject's fundus autofluorescence image(s) to the sponsor or designated reading center as soon as possible to confirm that the subject meets the inclusion criteria.

All subject's medical history shall be documented at baseline, and thorough investigation of any systemic condition shall be performed. In addition, to document and monitor the progression of the disease, in particular the atrophy size, historical retinal photographs (especially FAF) shall be requested from the subject and included in the subject clinical trial files. If possible, such files may be received from other sites where the subject had previously been seen, after proper authorization has been obtained.

Following screening activities and after receipt and analysis of all clinical laboratory results (excluding PK), all inclusion criteria and all exclusion criteria will be verified, and the subject will be determined to be either eligible or will be withdrawn from the study (screen failure). However, if a subject fails one entry requirement, if some clinical lab values were not properly tested (eg: due to a technical problem), or were inconclusive (eg. if the subject was not fasting at screening), or if retinal photographs or other baseline procedures were of insufficient quality, the investigator may choose to repeat the failed procedure (including re-test of laboratory value) to assess final eligibility.

If there are more eligible subjects than available spots for randomization, the sponsor will determine based on the investigator's recommendations who to randomize based on practical considerations (distance to clinical site, subject schedule, imaging quality, technical data acquisition, etc.). Non-randomized subjects will be withdrawn from the study as "screen failure".

If a subject is a screen failure but may be expected to meet all eligibility criteria in the future, subject may be rescreened upon agreement with the sponsor. Rescreened subjects will start the screening phase entirely, including getting a new screening ID number, and undergo the informed consent process again.

At the end of the screening activities, randomization, corresponding to the 1st administration of the study drug, should occur. Randomization should take place up to 40 days following the first screening activities, and as early as possible. Forty days are provided to the study team as a buffer to allow for example for (i) review of FAF imaging, (ii) determination of eligibility, (iii) review of clinical lab reports, (iv) determination of approximate compliance.

1.13.2 Randomization Visit (Day 1)

On the day of randomization ("Day 1" or V2), eligible subjects selected to participate in the treatment portion of the study are invited to return to the site (unless the medication is directly shipped to them). Subject receive a new "Subject ID" which is then used to replace the screening ID. Subject ID will be provided by sponsor or representative.

To randomize a subject, investigator is given a sheet containing the list of assignable medication ID (masked), and simply assigns the next available medication ID to the subject (this is possible because blocks and treatment assignment will already have been created at the time of production of the randomization list). The investigator should inform the sponsor in advance so that the site can be properly supplied with study drug. See section 1.9.4 for details. An online randomization portal may be used instead of the paper-based randomization code.

The first bottle(s) of study drug can then be dispensed to the subject. If sent by mail by the sponsor's representative, the site does not need to do anything. Otherwise, if the study drug is to be dispensed by the investigator or the clinical site pharmacies, subject should take the first dose in front of the investigator, and be observed for approximately one hour after taking the first dose before being discharged from the site.

As a guidance, investigators should dispense approximately 3 bottles (for a 3-month supply) at each visit.

1.13.3 Monthly check-up phone calls

The day after the first dose, the clinical staff should call the subject to check their well-being and remind them to continue taking the study drug at the same time every day (see section 1.9). The clinical staff shall then call the subject once a month to check for AE, remind subjects of compliance and of future visits.

1.14 SUBJECT RECRUITMENT, COMPLETION, DISCONTINUATION, WITHDRAWAL

1.14.1 Subject Recruitment

Identification: The investigator should use all IRB-permissible means to enroll subjects. The following three recruitment channels are suggested:

1. Walk-in visits from new patients
2. Patients referred by colleagues in other locations or practices,
3. Patients referred by the sponsor or representative
4. Check of investigator or clinical site's existing patients

Pre-screen assistance: Sponsor or representatives will be available to assist the investigator in, for example, the reviewing of de-identified retinal images or medical charts, for the purpose of identifying subjects who might meet the eligibility criteria.

Pre-qualification: Once a prospective subject has been identified, the investigator will reach out to the patient and follow an IRB-approved script to measure the interest of the patient for the study.

If a prospective subject expresses an interest to participate, the investigator will review the protocol requirements and eligibility criteria with the subject.

A pre-qualification health questionnaire, as the one typically used for standard practice in the investigator's office may be used by the investigator to pre-qualify subjects who could possibly meet the eligibility criteria. At that time, the investigator should use his/her best judgment so as to initiate screening only subjects he/she believes would not end up being a screen failure.

Screening: If the prospective subject remains interested and is deemed eligible, he/she will be invited for the screening visit. Informed consent will be obtained by the investigator.

1.14.2 Subject Completion; Early Discontinuation

Subjects must remain in the study for the 24-month duration of the treatment period to be considered to have "completed" the study.

Subjects who permanently discontinue treatment before completing the study will be considered to have gone through "early discontinuation". Subjects who temporarily discontinue treatment during the treatment period may be invited by the investigator to resume treatment, in which case a protocol deviation shall be noted.

1.14.3 Follow-up After Early Discontinuation

Subjects who permanently discontinue the treatment should be invited to return to the site as soon as possible, and within 1 month of the permanent discontinuation, for an "Early Termination" (ET) visit (see section 1.2). Unless instructed otherwise by sponsor, this ET visit should follow the schedule of V03 (short visits) in case of ET within the first 7 months of treatment, and the schedule of V04 in case of ET between 8 months and 24 months.

At the completion of ET, subjects should be withdrawn from the study and should return all study drug. There should be no additional follow-up visits.

Subjects who temporarily discontinue the treatment do not have any special follow-up and may simply continue the study with the planned schedule.

1.14.4 Temporary or Permanent Discontinuation of Treatment

Abrupt discontinuation of the treatment is not expected to affect subject health risks and therefore no special precaution is needed when discontinuing treatment. Sponsor shall be informed of any discontinuation of treatment.

- If investigator and sponsor both agree that it is not in the best interest of the subject to continue participation, for reasons including but not limited to, **non-compliance or health risk**, the subject shall discontinue treatment. Discontinuation may be temporary if the health risk is expected to resolve in a reasonable time. Subject may be allowed to resume treatment upon mutual decision by investigator and sponsor. In this case, off-treatment duration shall be documented.
- If subject's **treatment assignment is unmasked**, subject shall discontinue treatment, unless decided otherwise by sponsor.

- If one subject's levels of **either AST, ALT or Alk Phos is greater than 5 times the upper limit normal (>5x ULN)** for laboratory reference range, subject should discontinue the treatment immediately and permanently.
- If one subject's levels of **either AST, ALT or Alk Phos is greater than 3 times the upper limit normal (>3x ULN)** for laboratory reference range, subject should be re-tested within 2 weeks. Temporary discontinuation of treatment is not required, and decision shall be at the discretion of the investigator. If the subject is unable to be re-tested within 2 weeks, the subject should permanently discontinue the treatment. If at re-test, the re-tested values are lower than 3 times the ULN, the subject can continue or resume treatment. If at re-test the re-tested values are still higher than 3 times the ULN, the subject shall discontinue treatment, at least until these levels are measured to below 3 times the ULN. Once this is the case, subject shall be allowed to resume treatment only upon approval by sponsor.
- If a subject reports **pregnancy or if a subject's pregnancy test is positive,** subject shall immediately and temporarily discontinue treatment.
- If a subject's **QTc average value on duplicate ECG is greater than 500 ms**, the subject shall temporarily discontinue treatment. Subject may resume treatment only upon approval by sponsor.

If the subject discontinues due to an adverse event, pregnancy or other medical reasons as described above, the subject must be followed at regular intervals until the adverse event normalizes, returns to the subject's baseline condition, or is considered to be related to normal progression of the patient's condition or unrelated to the study drug. The sponsor and investigator will agree to an acceptable follow-up schedule for these subjects.

1.14.5 Lost to Follow-Up

Subjects will be considered lost to follow-up if the following occurs:

- Subjects misses 3 consecutive study visits (telephone and/or clinic visit), and
- Subject is unable to be contacted by telephone subsequent to the 2 consecutive missed visits (3 documented attempts by telephone within 2 weeks following the second missed visit), and
- Subject does not respond to the registered letter sent after the 3 attempted telephone contacts.

1.14.6 Withdrawal of Subjects from the Study

1.14.6.1 Reasons for withdrawal

A subject should be withdrawn from the study if either the following occurs:

- *Screening failure (before treatment start)*:
  - Subject has clinically significant abnormal lab results at screening, unless approved by sponsor and PI
  - Subject has QTc>460 msec for male or >480 msec for female at screening, unless approved by the sponsor and PI
  - The investigator or sponsor is in the opinion that subject would not be appropriate for the study, for reasons including not limited to, non-compliance, pre-existing condition or health risk.
- *Drop-out*:

- Subject withdraws consent

- *Treatment discontinuation:*
  - Upon permanent treatment discontinuation, subject should be withdrawn after being invited for a final follow-up visit, which should occur within 1 month of treatment discontinuation (see section 1.14.3).
- *Unmasking*:
  - A subject's study treatment assignment becomes unmasked to the subject, the clinical staff or the masked sponsor staff (except in the case of unintentional masking, in which case the sponsor and investigator will decide).
- *Lack of compliance*:
  - Subject is unable or has not complied with intake of the study medication, except when allowed by sponsor
  - Subject misses a follow-up visit window, except when allowed by sponsor
  - Subject becomes pregnant
  - Subject has undergone eye exam(s) outside the scope of this study that could affect the progression of the disease or the procedures or data collected in this study, except when allowed by sponsor (see 1.12.34.1)
  - Subject has received concomitant treatment that may affect the progression of the disease or the procedures or data collected in this study, except when allowed by sponsor.
- *Medical reasons*:
  - The investigator and sponsor both agree that it is not in the best interest of the subject to continue participation, for reasons including but not limited to, non-compliance or health risk.
  - Subject develops a medical condition that requires concomitant therapy with a prohibited medication (See section 1.11.3).
  - Subject develops a life-threatening adverse reaction, or a serious adverse reaction that places them at immediate risk.
  - Subject's levels of AST, ALT or Alk Phos are 3 times the normal upper limit, and if these levels are confirmed upon re-test on a fresh blood sample within 2 weeks
  - Subject's levels of AST, ALT or Alk Phos are 5 times the normal upper limit.
  - Subject experiences a prolonged QTc interval > 500 ms based on average QTc value of duplicate ECG, except if approved by sponsor
  - Subject is dead.
- *Lost to follow-up:*
  - Subject is lost to follow-up, after every reasonable effort has been made by the study staff to contact the subject and determine the reason for discontinuation/withdrawal. All efforts and measures must be documented.

1.14.6.2 How to withdraw a subject

If a subject is to be withdrawn from the study:

- subject is asked to stop taking the study medication,
- an early termination visit should be scheduled within approximately 1 month following the administration of the last dose of study medication (see section 1.14.3), and

- all remaining study medication should be returned to the site, including all empty bottle, used, or unused medications,
- investigator should make reasonable efforts to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights. All findings should be fully documented.

Upon withdrawal, the appropriate source document and CRF must be documented. All study medication returned by the subject should not be used or administered to another subject, except upon written request by the sponsor.

1.14.7 No Replacement of Subjects

Withdrawn subjects will not be replaced by new subjects, except upon written request by the sponsor. Therefore, it is important to only enroll participants who are likely to adhere to the schedule of the study visits, to the self-administered treatment regimen, and to the procedures performed during the study visits.

1.14.8 Data Collection

All data collected up to the day the subject was withdrawn will be used.

1.15 STATISTICAL METHODS

A statistical analysis plan (SAP) will be generated before data analysis and will describe all planned statistical analyses. The **SAP should supersede the below statistical sections of this protocol in case of discrepancies between such sections and the SAP.**

1.15.1 Sample Size Determination and Power Calculation

Sample size calculation was based on review of all available literature data on the progression of GA. With 300 subjects enrolled in the study and assuming that 80% of subjects are evaluable for the primary outcome measure, the study has an 80% power to detect, after 24 months of treatment, a 33% slowing in GA growth rate with a 2-tailed significance of 0.05, assuming a conservative standard deviation of 1.5 sqmm/year and an average GA growth rate of 1.8 sqmm/year in the control group.

As part of the exploratory measure, and assuming that 35% of enrolled subjects have a fellow eye with active or history of CNV, the study has an 80% power to detect, after 24 months, a 75% reduction in incidental progression to CNV in the study eye with a 1-tailed significance of 0.2 (Fisher's exact test).

1.15.2 Interim Analysis

Interim efficacy analyses, if any, will be performed according to the SMC charter and the statistical analysis plan. Safety data will be reviewed periodically by the SMC as described in the section below.

1.15.3 Safety Monitoring Committee (SMC); Interim Data Analyses

An independent SMC will be established to monitor the data on an ongoing basis and to ensure the continuing well-being of subjects enrolled in this study. The committee shall meet periodically to review safety data. The SMC may make recommendations about the study design or performance. A SMC charter shall supersede in case of conflict between this protocol and the SMC charter. The SMC shall be composed of at least 3 members, with no less than 2 voting members. To ensure proper masking of the study team, investigators, clinical staff, sponsor staff who interact with the investigators and/or subjects, cannot be members of the SMC. The SMC should consist of at least 1 medical expert in the field of ophthalmology and at least 1 statistics expert. SMC members may be amended from time to time.

The SMC will convene at designated time points but no less than once yearly. SMC may organize ad hoc meetings if required, or may change the frequency of meetings based on findings, enrollment or other factors. SAEs will be communicated on an ongoing basis to the SMC. The SMC may have access to unmasked data upon request and review tabulated summaries and any additional data the SMC may request during the study. The sponsor, representative and monitors should review masked data from the sites and notify the SMC of any issues relevant to subjects health. In no event should current or former SMC members communicate unmasked data, results, analyses or randomization code to anyone outside of the SMC.

Content of summaries, SMC role and responsibilities and general procedures, including communications and recommendations on the study conduct, will be defined and documented in the SMC charter.

1.15.4 Datasets

Analyses should be performed on the following datasets as appropriate and as described in the Statistical Analysis Plan:

- *Intent to treat (ITT)*: All randomized subjects who receive at least one dose of the study drug.
- *Per protocol (PP)*: All randomized subjects who have completed the study with no major protocol deviations or violations. Major deviations or violations are those believed to have a severe effect on the study endpoints. Decision as to whether a subject is included in the PP group will be taken after all data has been verified and before data analysis. Such decision should be properly documented.

1.15.5 General Principles

Individual subject data will be presented in the data listings. The listings shall include all subjects who were randomized and may exclude all the other subjects.

Summary statistics will be used to describe:

- *Continuous data*: the number of observations (N), mean (mean), standard deviation (SD), median (median), minimum value (min), and maximum value (max). The precision of the measurement unit for each variable will be used to determine the number of decimal places used to report those summary statistics. Min and max will be reported with the same precision. Mean and median will be reported to 1 greater decimal place, and the SD to 2

greater decimal places. Values that require conversion will be converted with the appropriate precision.
- *Categorical data* will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Missing or incomplete data will be handled as described in the Statistical Analysis Plan.

1.15.6 Demographics and Baseline Characteristics

Treatment groups will be described and compared with respect to demographics and baseline characteristics (including for example: age, sex, race, weight, height, genotype, phenotype, GA lesion characteristics, microperimetry, smoking status, etc.). The Statistical Analysis Plan will provide details on all analyses.

1.15.7 Safety Analyses

Safety data will be assessed by summarizing the number and proportion of subjects with and the types of AEs, using standard coding. The following are guidelines on how the information information will be analyzed. Variations are acceptable, for as long as the final report is representative of available data. The Statistical Analysis Plan will provide details on all analyses.

1.15.7.1 Adverse events

The verbatim terms of the AEs used by the investigator will be coded using the MedDRA dictionary on the eCRF. All reported AEs with onset (or worsening) during the treatment period, i.e. AEs experienced by subjects who have received at least one (1) dose of study drug (treatment emergent AEs or TEAEs) will be included in the analysis. AEs reported prior to the first administration of the study drug will be considered part “medical history”. For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, discontinue treatment due to a TEAE, or who experience a SAE.

1.15.7.2 Clinical Laboratory Tests

Laboratory data will be summarized by analyte. Descriptive statistics will be calculated for selected laboratory analyte at screening and at each scheduled time point.

1.15.8 Pharmacokinetic Analysis

Collection of plasma samples: After venipuncture, blood sample must be kept on ice until it is spun down and plasma is extracted. Extraction of plasma should occur within one hour of venipuncture. Plasma must be stored in amber glass vials and stored frozen at -20C and shipped regularly to the bioanalytical lab, as instructed by sponsor or representative. *Details are provided in the bioanalytical manual*.

Analyses: The following metabolites of vitamin A (non-deuterated) and ALK-001 (deuterated) will be measured by a bioanalytical lab throughout the study: retinol, retinyl palmitate, retinoic

acid. Data will be summarized and presented in plasma absolute concentrations (ng/mL) as well as in % deuterated.

1.15.9 Efficacy Analyses

As primary endpoint, we will evaluate the growth rate of geographic atrophy between baseline and 24 months. The study is powered to detect a ~33% reduction in the growth rate of atrophy between placebo and ALK-001. The Statistical Analysis Plan (SAP) will provide details on analysis techniques, and provide statistical code. The SAP will be submitted to the regulatory authorities before analyses are performed.

1.16 ADVERSE EVENTS REPORTING

Timely, accurate and complete reporting and analysis of safety data are crucial for the protection of subjects, investigators and the sponsor, and are mandated by regulatory agencies.

1.16.1 Definition of Adverse Events

Definition. An adverse event (AE) is defined as any untoward medical occurrence in a subject during the study, whether or not it is considered to be caused or related to the study drug. When an AE has been detected, the AE severity, causality relative to study treatment, action taken relative to study treatment, and outcome, must be reported.

Examples of AE. AEs include the following, when occurring after the start of treatment:

- A clinically-significant abnormality in physical or ocular examinations
- A clinically significant finding in ECG, vital signs
- A subject-reported symptom, injury, or disease
- A preexisting condition that has increased in severity, frequency or pattern after the start of treatment, unless this increase in severity, frequency or pattern is judged by the investigator as consistent with the natural progression of the preexisting condition.
- For abnormal laboratory values, check section 1.16.1.4 to determine if such abnormality is considered an AE

Planned/elective hospital admissions or surgical procedures (1.16.1.6) should not be considered adverse events.

1.16.1.1 Collection and Documentation of Adverse Events

Collection and follow-up of AE should occur according to the events table (Section 1.2). Clinical staff should inquire whether any AE has occurred through non-directive, non-leading questioning. AE may also be spontaneously reported by subjects during or between visits, while performing physical or ocular examination, reviewing clinical laboratory or ECG results, or other assessments. Information on all AEs should be recorded immediately in the source documents. Whenever possible, a constellation of signs and/or symptoms should be identified as one overall AE or diagnosis. Usually, not all information regarding the AE is available at the time the AE is detected (eg: AE outcome, or action taken, or causality to study treatment). Such information should be recorded as soon as it becomes available. See section 1.16 for details.

For each AE, clinical staff should record:

- Description of the event
- Start Date/Time
- Is the AE ongoing or not?
- End Date/Time
- Is the AE "serious" or "not serious" (see section 1.16.3)
- AE severity (see section 1.16.1.7)
- Frequency/Pattern (Single event, Intermittent, continuous)
- Action taken related with study treatment (see section 1.16.1.9)
- Action taken unrelated with study treatment (see section 1.16.1.11)
- AE outcome (see section 1.16.1.10)
- AE causality to study treatment (see section 1.16.1.8)
- Did AE cause subject to withdraw from the study?

1.16.1.2 *Preexisting Condition*

Preexisting condition known or discovered at screening. A preexisting condition is one present prior to or identified during the screening period, before the first study drug is administered. *Preexisting conditions should be recorded as "Medical History".*

Clinically-significant abnormality during the screening period. Any clinically-significant abnormality (eg: lab value, EKG, physical exam, etc.) found during screening should be recorded as part of the subject's medical history.

Changes in a condition marked as preexisting condition. During the treatment period, a condition previously recorded as a preexisting condition should then be recorded as an AE if the frequency, intensity, or the character of the condition worsens after the administration of the first dose of study drug, or if any new clinically-significant findings/abnormalities that meet the definition of an AE are observed. Progression of the disease consistent with the disease natural history shall not be considered an AE.

Preexisting condition discovered during the treatment period. As patients may sometimes omit to report, and the investigator may not have detected all preexisting conditions during the screening period, such preexisting conditions discovered after the treatment period has started, shall also be recorded as part of the subject's "Medical History".

1.16.1.3 *Post-treatment AE*

At the end of treatment, all unresolved SAEs, or any unresolved AEs judged by the investigator to be "related to the study drug" should be followed by the investigator until the events are resolved, return to baseline, become stable or a chronic condition, or the subject is lost to follow-up.

At the last scheduled visit, the investigator should instruct the subject to report any future event(s) that may possibly be related to the study treatment, according to the subject or the subject's personal physician.

The investigator should notify the sponsor of any death or AE occurring at any time after a subject has discontinued or terminated study participation, as long as such event may be possibly related

to the study drug. The sponsor should also be notified if the investigator becomes aware of the development of cancer.

1.16.1.4 *Abnormal Clinical Laboratory Values*

Non-drug related laboratory abnormalities occur spontaneously in clinical trials [99-101]. For example, the probability of a random elevation of AST, ALT, AP to two times the upper limit of normal is 0.67% in one given subject; this probability of random elevation becomes 13% in a trial of 20 subjects, 18% with 30 subjects and 28% with 50 subjects [101]. Therefore, a clinical laboratory abnormality should be documented as an AE only if:

- The abnormality induces clinical signs, suggests a disease and/or organ toxicity that is new or has worsened from screening, or
- The abnormality is of a degree that requires a therapeutic intervention or active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, and further diagnostic investigation.

1.16.1.5 *Pregnancy*

Pregnancy is not considered an AE.

Subjects enrolled in the study are 60 years old and over and should not be of childbearing potential. However, in the unlikely case a subject becomes pregnant during the study, the subject must immediately and permanently discontinue the study drug. All reports of pregnancy of female subjects or male subject's female partner must be reported to the sponsor within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (eg: spontaneous abortion, stillbirth, congenital anomaly) are considered SAEs and must be reported.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

1.16.1.6 *Hospitalization, Prolonged Hospitalization or Surgery*

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery shall be reported as an AE in the case diagnostic or elective surgical procedures for a preexisting condition.

1.16.1.7 Adverse Event Severity

The investigator must determine and record the severity of all AEs and SAEs.

Only after an event has been deemed to be classified as AE (see above section), the investigator will use the most up to date version of the Common Terminology Criteria for Adverse Events (CTCAE) for grading the severity of adverse events. Adverse events of CTCAE Grades 4 and 5 should be documented as "life-threatening". A copy of the CTCAE will be provided.

AE that do not appear in the CTCAE should be determined according to the following definition:

• Mild (Grade 1): Awareness of the event; may cause minimal interference with the subject's daily life; requires minimal or no treatment.
• Moderate (Grade 2): Discomfort enough to cause a noticeable impact on the subject's daily life; results in a low level of inconvenience or concerns with the therapeutic interventions.
• Severe (Grade 3): Incapacitation or significant impact on the subject's daily life; may require systemic drug treatment or other treatment.
• Life-Threatening (Grade 4): Subject in immediate risk of death from the event as it occurs.

1.16.1.8 Adverse Event Causality

The investigator must assess the relationship of the study treatment in causing or contributing to the AE using the following criteria:

• Unrelated: This relationship suggests no association between the study treatment and the reported event. Another factor is clearly involved.
• Unlikely: This relationship suggests a disease, other drugs or other factors may have produced the event; event may or may not follow a plausible temporal sequence with the study treatment; there is insufficient or contradictory information about the event which prohibits a proper assessment.
• Possible: This relationship suggests that the study treatment contributed to the AE; the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study treatment, but could also have been produced by a disease, other drugs or other factors; information on drug withdrawal may be lacking or unclear.
• Probable: This relationship suggests that the study drug has caused the AE. A reasonable temporal sequence of the event and the study drug administration exists. This assessment will be based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the investigator's clinical experience.
• Definite: This relationship suggests that a definite causal relationship exists between the study drug administration and the AE. Other conditions (concurrent illness, progression of disease state, or concurrent medication reaction) do not appear to explain the event.

1.16.1.9 *Study Treatment Action Taken*

The investigator must classify the study treatment action taken with regard to the AE. The action taken should be classified according to the following categories:

• Interrupted (Temporarily discontinued): Study drug administration temporarily stopped in response to an AE. If study drug administration is not-restarted, "action taken" changes to "withdrawn".
• Withdrawn (Permanently discontinued): Study drug administration permanently discontinued in response to an adverse event.
• None: Study drug dose not changed in response to the adverse event.
• Not Applicable: Action taken regarding study drug administration does not apply (for example in circumstances such as when the subject has died, or the treatment has already been completed before the adverse event).

• Unknown: Action taken is unknown (for example for a subject treated at a hospital not under the care of the investigator and investigator has no knowledge whether study drug was continued or not).

1.16.1.10 *Adverse Event Outcome*

The investigator must document the outcome of the adverse event using the following categories:

• Recovered/Resolved: Resolution of an AE with no residual signs or symptoms.
• Recovered/Resolved with Sequelae: Resolution of an AE with residual signs or symptoms.
• Recovering/Resolving: The AE is ongoing and continuously improving but is not fully resolved.
• Not Recovered/Not Resolved: The AE is ongoing and does not show any sign of improvement or no improvement.
• Fatal: Outcome of an AE is death (when death is at least possibly related to the adverse event).
• Unknown: Outcome of an AE is unknown (for example when a subject is treated at a hospital not under the care of the investigator and the investigator has no knowledge of the outcome of the adverse event).

1.16.1.11 *Treatment Given*

The investigator will describe whether any treatment was given for the AE. Treatment may include other medications, hospitalization, surgery or physical therapy. If medication was used, the generic name, dose, duration, and frequency should be provided.

1.16.1.12 *AE Collection and Reporting Period*

Adverse events will be collected regardless of the suspected cause of the event. The AE collection and reporting period is the period during which AEs must be reported, defined as the period starting from the administration of the first study dose until the end of the final visit. Any event that occurs prior to the first dose of study drug but after the signing of the informed consent will be recorded as medical history.

1.16.2 Medical Monitoring by the Investigator

It is the responsibility of the investigator to oversee the well-being of subjects enrolled at his/her site. However, PI and study staff is encouraged to discuss any potential general patient safety issue with the sponsor. Similarly, the sponsor will contact the investigator to clarify any pending health risk question.

1.16.3 Serious Adverse Events

A serious adverse event (SAE) is any AE whose outcome meets any of the following criteria:

- **Fatal** (death, regardless of cause, which occurs during participation in the study, or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug);
- **Life-threatening** (subject was at immediate risk of death; laboratory abnormality of Grade 4 are not SAEs unless the clinical status of the subject indicates a life-threatening AE);

- **Requires inpatient hospitalization or prolongation of hospitalization (**with the exception of planned/elective hospitalization);
- Results in:
    - **Persistent or significant disability or incapacity** (disability defined as substantial disruption of a subject's ability to conduct normal life functions);
    - **Congenital anomaly or birth defect;**
    - **An important medical event** clearly of major clinical significance although it may not be immediately life-threatening. An important medical event may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered important medical events.

"Severe" adverse events are not necessarily serious adverse events. Severe indicates the severity grade of the event (see section 1.16.1.7), such as in a mild, moderate or severe headache. Headaches are of minor medical significance and would not be considered to be serious adverse events. Serious adverse events are defined by the outcome of the event, outcome that pose a threat to a subject's life or functioning.

1.16.3.1 Reporting of Serious Adverse Events by Investigators

Investigators will record all SAEs on the SAE report form provided by the sponsor. The information collected will include at minimum the following: subject date of birth, age at the time of the onset of the SAE, sex, weight, outcome(s) attributed to the SAE, onset and stoppage date, location the SAE took place, whether the SAE was unexpected, a narrative description of the event (including relevant signs/symptoms, progression, treatment, outcome), relevant tests/diagnoses, other relevant medical history, medications used at the time of the SAE, relatedness to study treatment, action taken related to study treatment, rationale as to why the event is considered serious. Copies of relevant records should be added to the form, with all confidential or identifiable information removed. The subject ID and initials should be written on such records. Follow-up information on the SAE may be requested by the sponsor.

The SAE report form must be communicated to the sponsor within 24 hours from the point in time when the investigator becomes aware of the SAE. If not all information is available at the time the SAE report is made by the investigator, follow-up information should be submitted within 24 hours of their receipt.
Report SAEs by phone and fax to:

[redacted]

Such contact information may be amended from time to time, the latest information being found in the site study binder.

1.16.3.2 Investigator reporting: notifying the site or central IRB

The investigator will abide by his or her institution's specific IRB notification rules concerning the reporting of AEs and SAEs.

1.16.3.3 Sponsor reporting: Notifying the FDA

Following the receipt of the SAE report and whenever required by 21 CFR 312.32, the sponsor will report the event to the FDA on form 3500A and will send a copy of the form to the investigator. The investigator will keep a copy of this form 3500A on file.

Whenever required by law, the sponsor will report certain study AE to the FDA in IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening, and

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting:
If available, the sponsor will identify in the IND safety report all previous reports concerning similar AEs and will analyze the significance of the current event in light of such previous reports.

1.16.3.4 Sponsor reporting: Notifying participating investigators

The sponsor will notify all participating investigators, in a written IND safety report, of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, the sponsor will analyze the significance of such event in light of previous reports, if available.

1.17 ADMINISTRATIVE REQUIREMENTS, DATA HANDLING AND RECORD KEEPING

1.17.1 Trial-Specific Materials

Without limitations, trial-specific materials will include the following:

- This protocol

- Investigator brochure
- Manuals of operation (MOO)
- Clinical lab and Bioanalytical lab manuals
- Template source documents
- Informed consent forms
- PRO questionnaires if applicable
- Instructions for randomizing the study drug
- Randomization lists
- Regulatory binder and its contents
- Other study-essential documents

1.17.2 Modifications/Amendments to the Protocol

No modifications to the protocol should be made without the approval of the sponsor. Changes that significantly affect the well-being of subjects, the scope of the investigation, or the scientific quality of the study, such as safety or efficacy assessments, will require IRB notification prior to implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Minor changes can be implemented immediately after they have been approved by the sponsor. All changes must be documented in the regulatory binder. The sponsor will be responsible for submitting all protocol revisions to the FDA and other applicable regulatory agencies.

1.17.3 Publication Plan

No publication or disclosure of the study results is permitted, in whole or in part, except to the extent allowed in a separate written agreement, such as the applicable Clinical Trial Agreement between the investigator and the sponsor.

1.17.4 Clinical Study Report

A clinical study report (CSR) following FDA or ICH guidelines, will be prepared and submitted in accordance with local regulations.

1.17.5 Subject Privacy; Authorization to Use and Disclose PHI

The investigator will attempt to assure that subjects' confidentiality is maintained within the limits of the law. All CRFs, CSR, lab reports, study documents, and communications relating to the study, shall not ordinarily identify subjects by their full first and/or last name, but rather be limited to subject ID, initials, and date of birth.

As required by federal regulations, the investigator will allow the sponsor and/or its representatives, access to all pertinent medical records and source documents, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation for inspection.

For the proper conduct of the study and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and local privacy regulations, subjects enrolled in the study will need to provide continuous authorization to allow disclosure and use of their protected health

information (PHI). This authorization to use and disclose PHI may be given as part of a separate document or as part of the informed consent form, and must clearly specify which parties will have access to a subject's PHI, for what purpose and for how long.

1.17.6 Monitoring and Access to Medical Records

Study progress will be monitored by the sponsor or its representative (eg: a contract research organization) as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and to determine that the study is being conducted in conformance with accepted regulatory requirements. Arrangements for monitoring visits at each site shall be made with reasonable advance notice, except in case of emergency.

During a monitoring visit, the investigator or clinical staff must make office and/or hospital records of study subjects fully available for inspection, verification and copying by the sponsor or its representative.

If the sponsor or its representative is exposed to a subject's medical records or information, the sponsor will comply with all applicable laws and institutional policies regarding the confidentiality and privacy of such records and information, including but not limited to the HIPAA.

1.17.7 Source Documents

1.17.7.1 Definition

Source documents include all information, **original** records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents must be:

- **Attributable**: it should be clear who completed the source document
- **Contemporaneous**: the source data should be documented in "real time", as it is acquired. Acceptable amount of delay should be defined and justified
- **Accurate**: data should be a real representation of facts
- **Original, legible, enduring, complete, consistent, credible**, and if possible, **corroborated** (backed up by evidence)

Copies, **scans or transcriptions,** if certified after verification as being accurate and complete can also be considered source.

Adequate records of such source data will be maintained for the study. All original source documentation will remain at each investigator's site. Source data are stored by the investigator in any electronic medical records system typically used at the study site, including measurements that are obtained electronically, which will be printed and retained in the study files.

For more information on "good documentation practice in clinical research", please refer to [102].

1.17.7.2 Examples of source documents

Non-exhaustive examples of these original documents, and data records include: signed informed consents, lab reports, ERG traces, digital fundus files saved on the original hard drive, digital results of microperimetry saved on the computer used to acquire the data, medical notes on ocular

exam, receipt log of drug supply, protocol deviations, work sheets, nursing notes, adverse events reports, check-up phone call logs, information regarding withdrawal, reasons for discontinuation, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the clinical laboratories, and at the reading center involved in the trial.

1.17.7.3 Source document templates provided by sponsor

For each visit, the sponsor may provide template source documents to facilitate the flow of procedures, collection of data, and to help reduce the amount of source document. These source document templates can be used as primary source documents to standardize the format across all sites and facilitate transcription of source data into online case report forms (CRF).

These templates are only guidance and should not preempt the investigator from inserting any additional source document as required for the performance of the trial. If there are any discrepancies between the template and the protocol, the protocol shall govern.

If a procedure was not performed or the question was not asked or answer, use "Not Done" or "Not answered" as appropriate. If the item is not applicable to the individual case, write "Not Applicable". All entries should be printed legibly, preferably in black ink. If any entry error has been made, to correct such error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **DO NOT ERASE OR WHITE OUT ERRORS**. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

1.17.8 Case Report Forms

CRF will be designed in a user-friendly format to facilitate transcription and minimize risks of errors. All data requested on the CRF must be recorded. All missing data must be explained. Electronic CRF forms (eCRF) will be used in this study and stored on a server compliant with all FDA regulations on electronic data.

1.17.9 Case Report Form Completion, Data Storage and Transmission

After each visit or whenever new data have been collected for a specific subject, the investigator or designated representative shall record all clinical data required by the sponsor into electronic case report forms (CRF). CRF will be stored online in a secure electronic database. The sponsor will provide training of the database software (called electronic data capture or EDC) to permit site personnel to enter or correct information on the CRFs. Sponsor or representative may assist sites to input trial data in the CRF.

If required by the sponsor, a scan of the source documents, with erased directly identifiable information (such as name or hospital record number), shall be uploaded on the EDC to facilitate monitoring.

Transmission of all data into the CRF should preferably be completed within 5 business days of the visit or data collection, in particular at the earlier stages of enrollments. It is the investigator's

responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Any unexplained missing data will result in electronic queries by the study monitor(s) or sponsor.

The EDC application is password protected and contains an audit trail that records users and the date and time of initial inputs and of any correction.

Once data have been source-data verified (SDV), the investigator must sign off on the data by providing formal approval of all the information in the CRF to endorse the final submitted data for the subjects for which he is responsible.

At the end of the study, CRF data and corresponding audit trails will be retained by the sponsor. A copy of the final archival CRF in the form of a compact disk (CD) or other electronic media may be provided to the site and placed in the regulatory binder.

1.17.10 Record Retention

The investigator is responsible to retain study essential documents, sources and CRFs, for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country, or at least 2 years after the formal discontinuation of clinical development of ALK-001. These documents should be retained for a longer period if required by an agreement with the sponsor. The sponsor should inform the investigator/institution as to when these documents no longer need to be retained.

Should the investigator withdraw his responsibility to maintain the study records, he/she must place them in safekeeping and inform the sponsor of their location and contact information for the person/entity assuming responsibility for them.

1.17.11 Deviation from the protocol

The investigator shall not deviate from the protocol without prior approval from the sponsor, unless such deviation is necessary to manage a medical emergency. IRB approval may be requested if required by the site's IRB.

Each and all protocol deviations should be documented in an appropriate "*protocol deviation form*", showing at least the dates of and the reason for the deviation. A note-to-file or communication between the investigator and the sponsor may be added to the study file as further documentation of the deviation. All protocol deviations shall be listed in a "*protocol deviation log*".

In case a medical emergency requires a protocol deviation, the investigator shall notify the IRB and the sponsor of such protocol deviation as soon as possible. Such notice shall be given in no event any later than 5 working days after the emergency occurred, or shorter as applicable by law or local regulations.

1.17.12 Site or Trial Termination

For reasonable cause, the investigator, IRB, SMC, or sponsor, may terminate the study at a given site or at all sites. Conditions that may warrant termination include but are not limited to:

- Investigator non-compliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Delayed or poor communication between the sponsor and the investigator
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by FDA or other regulatory authority

Written notification that includes the reason for protocol or site termination is required.

1.17.13 End of Trial

For regulatory purposes, the "end of the trial" is defined as database lock, unless a different time is announced by the sponsor.

1.17.14 Ownership/Confidentiality of study data and documents

Any and all scientific, commercial and technical information disclosed by the sponsor to the investigator is considered confidential and proprietary property of the sponsor, and is bound by the confidentiality agreement between the sponsor, the site, the investigator and the study team.

The investigator understands that the information developed from this clinical study will be used by the sponsor in connection with the development of the study drug, and therefore may be disclosed by sponsor to other clinical investigators, the FDA, or to other government agencies. The investigator also understands that, in order to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide the sponsor with *complete test results and all data* developed during the performance of this study.

1.18 STUDY MONITORING, AUDITING, AND INSPECTING

1.18.1 Monitoring Plan

The sponsor will perform on-site monitoring visits as frequently as necessary, following a risk-based approach, and as detailed in a monitoring plan. A draft monitoring plan is found in section

Monitoring shall be performed to ensure adherence to good clinical practices, to the protocol, and to ensure quality of the collected data.

The monitor will record dates of the visits in a study site visit log kept at the site. At each visit, the monitor will review the study document, including the study binder, source documents, patient records and all study-essential documents.

All source documents, their nature and location will be identified to ensure that the monitor is aware of all source documents and has access to them for verification. The investigator and the clinical team will allocate sufficient time for and be accessible during such monitoring activities, and will ensure that the monitor has suitable space and time to conduct the monitoring visit.

After the monitoring visit, the monitor will send a report to the investigator with findings.

A draft monitoring plan is found in section 1.22.5.

1.18.2 Auditing and Inspecting

Investigators will permit study-related audits and inspections by the sponsor or authorized auditors, the IRB, or government regulatory bodies, of all study-related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). Investigators will guarantee direct access to these documents and support at all times for these activities. Medical records and other study documents may be copied during the audit or inspection, provided that subject names and other private information are masked to preserve confidentiality.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection, and the sponsor should be allowed to be present during such inspection.

1.19 ETHICAL CONSIDERATIONS

1.19.1 GCP conduct of the Trial

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

1.19.2 Institutional Review Board

This protocol and any amendments will be submitted by the sponsor or by each site's study team, to a properly constituted Institutional Review Board (IRB) for formal approval of the study conduct at the site. Each IRB should be in compliance with the general standards for composition, operation, and responsibility of an IRB set forth in ICH guidelines for GCP Sections 3.1 to 3.4 and 21 CFR part 56. A central IRB can be used.

The investigator in collaboration with the sponsor or representative, shall be responsible for reporting to the IRB all changes in research activity, including protocol amendments, updates of Investigator's Brochures, investigational new drug (IND) safety reports, all unanticipated problems involving risks to human subjects, study termination, and other reporting required by the IRB . The investigator will also be responsible for submitting progress reports and annual renewal reports to the IRB at regular intervals appropriate to the degree of subject risk involved, but no less than once per year.

Copies of all IRB notifications and approvals by the IRB, including approved informed consent or assent form(s), shall be included in the regulatory binder, and provided to the sponsor. The investigator should also provide a current list of all IRB members after all submissions.

1.19.3 Subject Information, Informed Consent

General information: Informed consent must be obtained from each subject before starting to perform any protocol-related activity. The informed consent form (ICF) shall first be approved by the sponsor prior to its submission to the IRB. The ICF will comply with all applicable regulations governing the protection of human subjects.

Only the investigator, or appropriately-trained designee shall be authorized to obtain informed consent. The name of any investigator-appointed designee should be provided to the sponsor in a delegation log, and appropriate training documentation kept in file.

Informed consent process*:* All prospective study subjects of age of consent will be provided the IRB and sponsor-approved ICF describing this study and providing sufficient information to make an informed decision about participation in this study. The investigator or authorized designee must explain the nature of the study and the treatment in such a manner that the subject is aware of his/her rights and responsibilities, as well as potential benefits and risks. The study team shall also answer any questions that might arise throughout the study and share any new information, in a timely manner, that may be relevant to the subject's willingness to continue his/her participation in the trial.
Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Sufficient time should be given for prospective subjects to review the ICF and ask questions. Once all of their questions have been answered and they have voluntarily agreed to participate in the study, subjects will be asked to sign and date the ICF. Documentation of the discussion and the date of informed consent must be recorded in the subject's medical record or a study/clinic chart. Subjects who cannot give informed consent (i.e., mentally incompetent patients or those physically incapacitated) are not to be recruited into the study. Subjects who are competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian.
A printed copy of all signed informed consent documents must be given to the subject.

1.20 STUDY FINANCES

1.20.1 Funding Source

This study will be funded by the sponsor.

1.20.2 Financial Disclosure / Conflict of Interest

The present study is a covered clinical trial. For compliance with regulations, all clinical investigators (PI) and sub-investigators (sub-I) directly involved in the treatment or evaluation of study subjects, who are not full-time or part-time employees of the sponsor, are required to provide the sponsor with sufficient accurate financial information to allow for complete disclosure or certification and to update this information if any relevant changes occur during the study and for one year following the study completion or the end of the PI or sub-I participation. The sponsor will provide a "financial disclosure form" to be filled out by PIs and sub-Is.

1.20.3 Subject Stipends or Payments

Upon IRB approval, subjects may receive gift cards to defray travel, hotel or other expenses associated with each visit. Each site's informed consent form will provide specific details and gift card amounts, which must be IRB approved.

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1.22 ATTACHMENTS

- Sample Investigational Drug Label
- Instructions on how to reduce vitamin A intake (to be distributed to each study participant)
- Vision questionnaire (VF-14)
- Functional Reading Independence (FRI)
- Draft Monitoring Plan

1.22.1 Sample Investigational Drug Label

("**CA27**" is an example of a random medication ID number, shown here only as an example). The label has a matte finish and **only ball pen** should be used to write on it (other types of ink will smudge or fade).

1.22.2 Instructions on how to reduce vitamin A intake

Instructions on How to Reduce Vitamin A Intake

What is vitamin A?
Vitamin A is necessary for your vision and mostly found in

- **Food**: milk, cheese, liver (including giblets, cod liver oil, pate), egg yolks, yogurt, butter, margarine, cereals and sweet baked goods (as they often contain butter and eggs).
- **Vitamin pills**: multivitamin pills and vitamin A pills

Which food items contain the most vitamin A?
Liver, giblets, cod liver oil, pate

Is there any vitamin A in fruits and vegetables?
Vitamin A is not found in fruits and vegetables. Fruits and vegetable contain provitamin A carotenoids. During this study you can consume fruits and vegetables without limitation.

What is ALK-001?
ALK-001 is a new form of vitamin A. It is being tested as a new drug for the treatment of certain forms of blindness. ALK-001 is an “investigational drug”, which means it is a drug still under investigation to see if it can treat a disease.

When should I take ALK-001?
You should take ALK-001 preferably in the evening, for example at dinner or at bedtime, whichever is more convenient for you. It is important that you take it daily and that you avoid missing a dose. However, if you miss a dose, take it as soon as you can remember, even if it is the next day or if it is close to the time you should take the next pill. Do not take more than 2 capsules in one day.

Why should I reduce my vitamin A intake?
Because ALK-001 is a new form of vitamin A, vitamin A contained in food or vitamin pills will interfere with ALK-001, reduce its activity and may result in undesirable side effects.

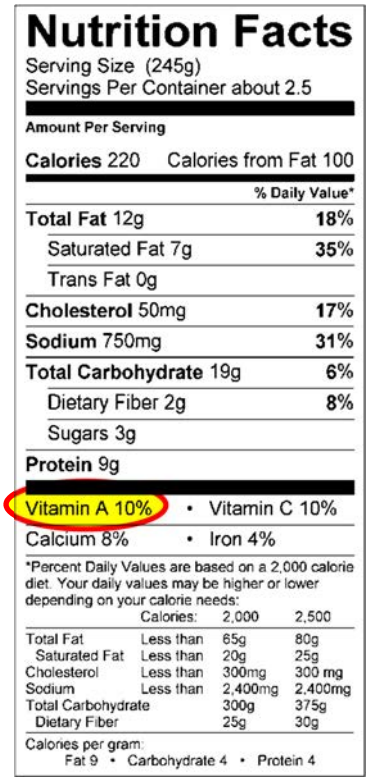
Is there any item I should not consume during the trial?
During the study, you should **never take**:

- Vitamins or supplements containing any Vitamin A
- Food items containing large amounts of vitamin A such as liver (including liver oil), pate, foie gras and giblets

Why do I have to get my blood drawn?
We will draw your blood at each visit to verify that you have been taking your ALK-001 pills properly, to verify that you are not pregnant and to monitor your health.

Will I lack vitamin A by reducing my vitamin A intake?
No. ALK-001 is a new vitamin A which supplies your body's vitamin A needs. As a result, you are not expected to become deficient in vitamin A.

How can I monitor how much vitamin A is in the food I am eating?
By reading food labels. Food labels will tell you how much vitamin A is in each serving (expressed in %). All food labels follow a similar design. The line that tells you about vitamin A content can usually be found towards the bottom of the label. Look for example at the label below. Vitamin A content is highlighted yellow.



Nutrition Facts

Serving Size (245g)
Servings Per Container about 2.5

Amount Per Serving

Calories 220 Calories from Fat 100

	% Daily Value*
Total Fat 12g	**18%**
Saturated Fat 7g	**35%**
Trans Fat 0g	
Cholesterol 50mg	**17%**
Sodium 750mg	**31%**
Total Carbohydrate 19g	**6%**
Dietary Fiber 2g	**8%**
Sugars 3g	
Protein 9g	

Vitamin A 10% • Vitamin C 10%
Calcium 8% • Iron 4%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Saturated Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300 mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

On this label, the vitamin A content is 10% per serving. This is a moderate amount. Some labels will state "Not a significant source of vitamin A", meaning that there is no vitamin A inside (= 0%).

The amount is always displayed in percent "%" and corresponds to a certain quantity of vitamin A contained in one serving of the food item.

When you buy something, do check the labels and try to buy items that contain the least amount of vitamin A.

As a rule of thumb, avoid buying any items that contain over 10% of vitamin A per serving.

How much vitamin A per day from food can I consume?
The lower the better. Try to limit your daily intake to “30%”, or 3 servings of vitamin A containing items. Millions of Americans already consume low amounts of Vitamin A in their normal, daily diet, so you may actually not even need to change your dietary habits.

How do I count the total number of servings of vitamin A I had in a day?

Most packaged food items come with a nutritional label. When you are about to buy an item, always check the label for vitamin A content.

If you purchase yogurt and milk which contain vitamin A and consume 1 servings of milk (~1 cup) and 1 serving of yogurt (1 container), your total intake will be 2 servings. You should try to keep your daily intake to under 3 servings per day.

I usually buy certain brands of milk, cereals, yogurt or oatmeal for example, but I have never checked the labels before. What should I do?
Next time you are in the grocery store, check the labels before you buy the item. If the label indicates it contains more than 10% of vitamin A per serving, try to search for a similar item that would contain a lower amount, ideally between 0% and 5% of vitamin A, and up to 10%. In our experience, you can nearly always find cereals, yogurt and oatmeal that are completely free of vitamin A.

Do almond, rice, soy or other nondairy milks contain vitamin A?
Usually yes. In the United States, these items are often fortified with vitamin A. Some brands however do sell vitamin A-free nondairy milks.

I have eaten more than 30% of vitamin A today. Is this a problem?
Not if it only happens rarely (a handful of times a month). However, try to keep your vitamin A intake within reasonable limits during the study.

I like drinking milk, eating cereal and eating lots of butter or cheese. Are there alternatives to these foods that have little vitamin A?
Yes. As you shop for food items, look at “nutrition facts” and find the vitamin A content. If you are unsure, ask someone to assist you in the shop. There are several brands of cereals, milk, butter that contain low amounts (less than 5% DV per serving) of vitamin A. Also look at the tables

below that provide a list of substitute food items that are free or have little vitamin A and can be consumed during the study. These items may not be available in your usual grocery store, so it is best if you look at individual labels in your store.

When eating out in a restaurant, what food should I avoid?
You should avoid all the food items listed on the next page as it is likely that the restaurant did not use vitamin A free alternatives. Ask the waiter to ensure these items are not in the dishes you are ordering.

Can I consume supplements containing vitamin A?
No. During the course of the trial, you must absolutely not take any supplement containing vitamin A or beta carotene as they will interfere with ALK-001.

7 Key Points to remember during the study:

1. Remember to take your ALK-001 medication daily, preferably in the evening at dinner or bedtime. Avoid missing a dose, but if you forget, take your dose as soon as you remember, even if it is on the following day and close to the next time you should take the pill. Do not take more than 2 capsules in a given day however.
2. Never take vitamin A or beta carotene supplements or eat liver-based products
3. Try to reduce your vitamin A intake from food to as low as you can, and maintain it at least below 3 servings per day of vitamin A containing food
4. Before buying a food item, always check the nutrition label to verify that its vitamin A content is less than 10% Daily Value (DV) per serving
5. Try to prefer brands that have close to 0% Daily Value (DV) vitamin A. Most food items have brands containing nearly 0% Daily Value (DV) vitamin A. Ask for assistance in the store in case you need help
6. Fruits and vegetables are safe to consume.

COMPLETELY BANNED DURING THE TRIAL:

- Liver
- Liver based products (Pate, liver sausage, liver oil)
- Foods that contain over 10% or more of the daily vitamin A per serving (as seen on the nutrition label)
- Giblets
- Vitamin A or beta-carotene containing pills (including multivitamins with vitamin A)
- Liver oil pills

PERMITTED DURING THE TRIAL WITH MODERATION
(UP TO 3 SERVINGS PER DAY OF FOOD ITEMS CONTAINING LESS THAN 10% DV VITAMIN A PER SERVING):

- Milk (regular, almond, soy, rice, dried, etc.)
- Yogurt
- Butter
- Margarine
- Cereals
- Oatmeal
- Egg yolk
- Sweet baked good (cookies, cakes)
- Cheese
- Cheese based products (Ricotta, Cottage Cheese, Cheesecake, Cream Cheese, Raviolis with cheese, cheese pizza, etc.)
- Cream
- Cream based products (Sour cream, etc.)
- Raviolis with cheese
- Pizza with cheese
- Waffles and pancakes

1.22.3 Visual Function VF-14 Questionnaire

Patient Name: _____ DOB: _____ Date of Visit: _____

VF-14 QOL Questionnaire

Because of your vision, how much difficulty do you have with the following activities?
Check the box that best describes how much difficulty you have, even with glasses.
If you do not perform the activity for reasons unrelated to your vision, circle "n/a"

Activity		None	A little	Moderate	Great deal	Unable to do
1. Reading small print, such as medicine bottle labels, a telephone book, or food labels	n/a	☐	☐	☐	☐	☐
2. Reading a newspaper or a book	n/a	☐	☐	☐	☐	☐
3. Reading a large-print book or large-print newspaper or numbers on a telephone	n/a	☐	☐	☐	☐	☐
4. Recognizing people when they are close to you	n/a	☐	☐	☐	☐	☐
5. Seeing steps, stairs or curbs	n/a	☐	☐	☐	☐	☐
6. Reading traffic signs, street signs or store signs	n/a	☐	☐	☐	☐	☐
7. Doing fine handwork like sewing, knitting, crocheting, carpentry	n/a	☐	☐	☐	☐	☐
8. Writing checks or filling out forms	n/a	☐	☐	☐	☐	☐
9. Playing games such as bingo, dominos, card games, or mahjong	n/a	☐	☐	☐	☐	☐
10. Taking part in sports like bowling, handball, tennis, golf	n/a	☐	☐	☐	☐	☐
11. Cooking	n/a	☐	☐	☐	☐	☐
12. Watching television	n/a	☐	☐	☐	☐	☐
13. Driving during the day	n/a	☐	☐	☐	☐	☐
14. Driving at night	n/a	☐	☐	☐	☐	☐

Patient Signature: _____

Office use only:	(C) *# checked boxes in column*					
	(F) *factored amounts*	X4 =	X3 =	X2 =	X1 =	0

C = total number of Checked boxes in column

F = sum of the Factored amounts

V =Final V-14 score

Final Score: (F _____ / C _____) x 25 = V

V = ☐

VF-14 QOL Questionnaire_10-28-09

MD Signature: _____

1.22.4 Functional Reading Independence Index (FRI)

The Functional Reading Independence Index (FRI Index)

Please read the following instructions to the patient.

Instructions to Patient:

We are interested in learning more about how your vision affects your everyday reading. I'm going to ask you about seven (7) activities that involve reading. If you wear eyeglasses or contact lenses, please answer all the questions as if you were wearing them during the activity.

Please take as much time as you need to answer each question. Remember, there are no right or wrong answers. All of your answers are confidential. Do you have any questions before we begin?

Please think about your vision over the past 7 DAYS when answering each question.

1. In the past 7 DAYS, did you read written print such as books, magazines or newspapers?	☐ Yes ☐ No
If "Yes"	**I'd like to know more about that. I will read you a list of statements – Please answer "Yes" or "No" to each:** a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the text closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? *(example, if needed:* using a large print book) ☐ Yes ☐ No e. Did another person help you read written print such as books, magazines or newspapers? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 2.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? Please choose one answer. *(Go to Question 2)*
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? Please choose one answer. *(example, if needed:* no time or opportunity to read written print*)*

2. In the past 7 DAYS, did you read to pay bills or write a check? ☐ Yes ☐ No	
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the bill or text closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No *(example, if needed:* using a check-writing template*)* e. Did another person help you read to pay bills or write a check? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 3.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 3)*
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to pay bills*)*

3.	**In the past 7 DAYS, did you read in order to take your medicine such as reading a prescription, medicine label, or a syringe?**	☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the medicine bottle or prescription closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read in order to take your medicine? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 4.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 4)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need to take medicines*)*	

4. In the past 7 DAYS, did you read labels such as price tags, food labels, or clothing labels?	☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the price tag or label closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read labels? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 5.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 5)*
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to read labels*)*

5.	**In the past 7 DAYS, did you make or receive a telephone call that required you to read the numbers on a telephone, answering machine or caller-ID device? This includes cell phones.**	☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting or less lighting? ☐ Yes ☐ No b. Did you move the telephone closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No *(example, if needed: using a "talking caller-ID")* e. Did another person help you read to make or receive a telephone call? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 6.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 6)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to make phone calls*)*	

6.	**In the past 7 DAYS, did you read words or numbers on your screen while watching television?**	☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use less lighting? ☐ Yes ☐ No b. Did you move closer to the television? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read words or numbers on the television screen? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 7.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 7)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to watch television*)*	

7. In the past 7 DAYS, did you read when using a computer? ☐ Yes ☐ No	
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use less lighting or change the contrast on the screen? ☐ Yes ☐ No b. Did you move closer to the computer screen or increase the font size? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read when using a computer? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to concluding statements.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to concluding statements)*
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to use a computer*)*

This concludes our interview. Thank you for your time.

1.22.5 **Clinical Trial Monitoring Plan (Draft)**

Clinical Trial Monitoring Plan (CTMP)

Alkeus Pharmaceuticals, Inc.

Draft

April 2018

This plan will be implemented to monitor the clinical sites approved for performance of this protocol under an Investigational New Drug (IND) application. Standard Operating Procedures for Monitoring Clinical Trials established by each study site of study, if existing, will complement the monitoring activities.
Monitoring will be performed by the sponsor or an alternative qualified Monitor.

Purpose of Monitoring Plan

The purpose of this monitoring plan is to present a potential approach to monitor the present clinical study. The plan complies with good clinical practice (GCP) guidelines (5.18.1), FDA guidelines and FDA regulations (21 CFR 312 and 812), which require monitors to verify that:

(a) the rights and well-being of human subjects are adequately protected.

(b) the reported trial data are accurate, complete, and identical to the source documents.

(c) the conduct of the trial is in compliance with the approved protocol, with GCP, and with applicable regulatory requirements.

This document identifies key monitoring activities and specifies the data to be reviewed over the course of the clinical trial. The monitor will conduct visits in accordance with this plan.

Scope of Monitoring

In compliance with GCP guidelines, monitors will verify that data collected on data collection forms (CRFs) match the source documents. Source documents are defined as any original records or data related to the trial or to subject treatment or medical history. Source documents include: original hospital, clinical, and office charts, laboratory notes, subject diaries or evaluation checklists, pharmacy records, recorded data from automated instruments, transcriptions (certified to be accurate after verification), magnetic media, or x-rays. *(GCP 1.5.2*)

The monitor will compare the practices and procedures of the investigator with the commitments made in the protocol and regulatory applications (e.g. IND, IRB). *(FDA Compliance Program Guidelines, Part III)*

The monitor's primary responsibilities (GCP 5.18.4) when relevant to the clinical trial are to:

3.1 Verify the investigator's adequate qualifications to safely and properly conduct the trial. To accomplish this, the monitor will:

- Review the study regulatory file to verify there is a CV or other documentation of qualification for each investigator.
- Verify that each CV was current at the time of study initiation.

3.2 Verify that facilities, including laboratories and equipment, remain adequate throughout the trial. To accomplish this, the monitor will:

- Verify the regulatory file contains current certifications and lab normal ranges for the laboratory performing protocol-required procedures or tests.

3.3 Verify storage, dispensing, instructions for use, and disposition of the investigational product complies with regulatory requirements.

DRUGS

The monitor will check the product disposition records, protocol, regulatory file, or subject files to:

- Assess whether the site stores the product under the conditions specified in product labeling or packaging.
- Verify that the protocol or the regulatory file documents how subjects are provided with necessary instruction on how to use, handle, store, and return product.
- Verify that the time the product has been stored does not exceed the shelf life specified in the labeling or packaging.
- Verify the site has documentation in the regulatory file of receipt of disposition/use and return of product.
- Verify the regulatory file contains manufacturer guidelines or other instructions for handling product.
- Verify the site maintains records that indicate product has been supplied only to eligible subjects at protocol specified doses.

3.4 **Verify that the site follows the approved protocol.** To accomplish this, the monitor will:

- Verify the (current) IRB approved protocol and the (current) protocol in the regulatory file are the same.
- Compare data to be collected on case report forms (CRFs) with the IRB approved protocol (data collection should not exceed the limits defined by the protocol).
- Verify the number and type of subjects entered into the study was confined to the number and type the protocol defined eligible.
- Verify that no deviations from or changes to the protocol have been implemented without prior review and documented approval of the IRB (except where necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.)
- Verify the labels on the individual patient bottles/medical devices comply with the requirements for investigational drug or device labeling.

3.5 **Verify that written consent was obtained before subjects' participation**. To accomplish this, the monitor will:

- Verify correct version of IRB-approved consent form was used.
- Verify the date the consent form was signed and dated.
- Verify, against the subject's medical record, source documentation that the consent was signed before any research test or procedure was performed.
- Verify the subject signed and dated a HIPAA form prior to enrollment, as applicable.

3.6 **Ensure trial staff is adequately informed about the trial and has not delegated responsibilities to unauthorized individuals**. To verify this, the monitor will:

- Note the identity of all persons and locations involved in the collection of data by looking at the Delegation of Responsibility Log. (FDA Compliance Program Guidelines, Part III) (If there is no site Delegation of Responsibility log, the monitors will require that one be completed and updated throughout the trial).
- Check documentation for information about distribution of the currently approved protocol and Investigator Brochure to the study team.
- Check documentation of any protocol specific training of authorized individuals.
- Compare study documents, the IRB application, and the Delegation of Responsibility log to determine whether responsibilities have been delegated to unauthorized individuals.

3.7 **Verify that only eligible subjects are enrolled**. To accomplish this, the monitor will:

- Verify whether the existence of the condition for which the investigational product is being studied is documented by a compatible history.
- Determine, when possible, whether the existence of the condition is documented by notation made prior to the initiation of the study.
- Compare the protocol inclusion/exclusion criteria against the subject's medical record, or other source documentation, to determine whether the enrolled subject is eligible for inclusion in the study.

3.8 **Report subject recruiting and enrollment rate**. To accomplish this, the monitor will:

- Count the number of subjects enrolled (defined by this plan as having signed a consent form) and compare this number to the limit approved by the IRB. (FDA Compliance Program Guidelines, Part III)
- Check subject screening/enrollment log to document subjects who entered pretrial screening but did not give consent to participate. (The enrollment log may be incorporated within the screening log.)

3.9 **Verify trial records are accurate, complete, and current**. To accomplish this, the monitor will:

- Verify the investigator or assigned designee has completed current CRFs – and that they are signed and dated appropriately.
- Verify source documentation was used to complete CRFs.
- Verify the protocol identifies source data that will be recorded directly on CRFs (with no prior written or electronic record of data).
- Verify whether clinical laboratory testing (including EKGs, X-rays, eye exams, etc.), as noted in the case report forms, is documented by the presence of completed records among the source documents. (FDA Compliance Program Guidelines, Part III)

- Verify the site's data and source documents in terms of their organization, condition, completeness, and legibility. (FDA Compliance Program Guidelines, Part III)
- Verify the investigator has made required reports and submissions to the IRB, Sponsor and, if applicable, the FDA.
- Verify the information in the reports to information in the Regulatory file and source documents to verify accuracy and completeness, including reports of any adverse experiences.

3.10 **Check the accuracy and completeness of CRF entries, source documents, and other trial-related records against each other**. To accomplish this, the monitor will:

- Verify the data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents.
- Verify any dose or therapy modifications are well documented.
- Verify adverse events, concomitant medications, and underlying illnesses are reported accurately on the CRFs, in accordance with the protocol.
- Verify CRFs reflect all visits that subjects fail to make and all tests or examinations that are not performed.
- Verify subject deaths, withdrawals, dropouts, and subjects lost to follow-up are reported and explained on CRFs.
- Verify, by looking at the CRF in the subject binder/folder, that all applicable forms are completely filled out if any subject has withdrawn or dropped out of the study since enrollment and that an explanation is provided.

3.11 **Inform the investigator of any CRF errors and ensuring appropriate corrections are made, dated, explained (if necessary), and initialed by the investigator or designee**. To accomplish this, the monitor will

- Inform the investigator of any CRF entry error, omission, or illegibility.
- Ensure that appropriate corrections, additions or deletions are made, dated, explained (if necessary), and initialed by the investigator or his/her designee authorized to make such changes. (This authorization must be documented on the site responsibility log).

3.12 **Determine whether all adverse events are reported appropriately**. To accomplish this, the monitor will:

- Verify that serious adverse events have been reported to the IRB, and, if applicable, Sponsor by looking at correspondence files and comparing against subject medical records. (FDA Compliance Program Guidelines, Part III)
- Verify, by reviewing correspondence files and comparing against subject medical records, that the reporting to the IRB of Unanticipated Problems has been followed according to the site specific IRB’s rules:

- Any serious event (including on-site and off-site adverse events, injuries, side effects, deaths or other problems) which, in the opinion of the local investigator, was unanticipated, involved risk to subjects or others, and was at least possibly related to the research procedures;
- Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur;
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
- Any publication in the literature, safety monitoring report (including Data and Safety Monitoring Reports), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
- Any breach in confidentiality that may involve risk to the subjects or others;
- Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the research staff; or
- Any other serious and possibly related event which, in the opinion of the investigator, constitutes an unanticipated risk.

- Verify, by looking at subject medical records, that events not meeting the reporting requirement are nonetheless captured on the IRB continuing review report.
- Verify that all adverse events that are required by FDA regulation to be reported to the FDA have been reported within the specified time frames.

3.13 **Determine all essential documents are maintained**. To verify this, the monitor will:

Verify that all applicable documents exist and are current as of date of monitoring. The following documents, if applicable, are essential documents:

- Transfer of Monitoring Obligation Agreement
- IRB, FDA, and other regulatory documents (e.g. reports, correspondence)
- Signed protocol
- Investigator brochure
- Consent form and IRB-approved information for subjects
- Randomization procedure
- Sample CRF or document stating medical record is data collection form
- Investigator and sub-investigators CV or documentation of qualifications & training
- Site signature log / Delegation of Responsibility Log
- Lab normal ranges
- Lab certifications
- Screening log
- Enrollment log
- Adverse event log
- Correspondence
- Subject code list

- Product accountability log
- Product handling and storage instructions
- Product shipping records and certificates of analysis
- Record of retained samples
- Decoding procedures for masked trials
- Record retention plan
- Monitoring reports

3.14 **Obtain copies of all study-related correspondence with the FDA, when needed**.

3.15 **Communicate deviations from the protocol, GCPs, or regulatory requirements to the investigator and taking appropriate action to prevent recurrence of the deviations.** To accomplish this, the monitor will:

- Verify subject visits have taken place as stated in protocol by checking the subject tracking log.
- Verify all tests have been completed as stated in the protocol by looking at source documentation and CRFs.
- Verify any noncompliance issues with protocol (subject) by looking at CRFs and other source documentation.
- Verify if any visit was out of allowable time deviation by looking at subject visit schedule.
- Verify any other deviations by comparing the protocol with source documentation and/or subject CRFs.

Extent of Data Monitoring
Monitors will review clinical data that affect study endpoints defined in the protocol. Data collected for reasons other than to support protocol-defined endpoints will not be monitored.

The extent of subject data monitoring will include verifying:

- Initial study consent : 100% of enrolled subjects;
- Study eligibility : 100% of enrolled subjects;
- Data to support protocol defined endpoints : 100% of completed subjects

In addition to monitoring subject data, the monitor will review the regulatory file for any additions to GCP-required documents since the last visit. Monitors will, at their first and last monitoring visits, review the regulatory file for the presence, completeness, and accuracy of all GCP-required documents.

Transfer of Monitoring Obligation Agreement
A signed Transfer of Monitoring Obligation Agreement will be obtained from all sponsors and principal investigators, if applicable.

Site Visit Confirmation
After scheduling a monitoring visit with the site the following will occur:

- The monitor will review previous monitoring reports to identify any unresolved issues.

Debriefing the Investigator
At the end of each monitoring visit, the monitor will meet with the investigator or coordinator to go over any findings of the visit.

Documentation of Findings
The monitor will send a monitoring report to the study sponsor and to the study investigator. A copy of every monitoring report will be retained by the sponsor and the monitor.

The monitoring report will describe the progress of the study, the findings of the visits, unresolved issues, and follow-up required. The monitor will keep an electronic copy of the report and a signed copy will be maintained in the Regulatory file. Follow-up items will be checked and documented at the next monitoring visit. The report will include, but will not be limited to, the following:

- A list of records reviewed, i.e. subject charts, hospital records, lab slips, etc.;
- Number of case report forms reviewed by research subject number and visit date;
- Statement that test article accountability records were or were not sufficient;
- Statement regarding whether there was any evidence of under-reporting of adverse events;
- Statement regarding protocol adherence

(FDA Compliance Program Guidelines, Part III)

Frequency of Visits
The monitor will provide monitoring before, during, and at the end of clinical trials.

In general, monitoring visits should be scheduled according to a "risk-based monitoring" approach as found in FDA guidance (August 2013).

The following schedule can be used as a suggestion:

- *Site Initiation Visit (SIV):* After IRB approval but prior to enrolling the first subject;
- *First monitoring visit*: As soon as possible after the first subject is enrolled;
- *Risk-based interim monitoring visits (IMV):* as needed based on risk, or about 3 weeks after first subject is enrolled;
- *Close-out visit (COV):* After the last subject has completed his/her participation in the study.

This monitoring schedule may be revised based on the following considerations:

- Accrual rate
- History of protocol deviations or non-compliance with GCPs
- Number of data corrections required
- Study stage (e.g. start-up or follow-up)
- Complexity of the trial
- IRB request

Interface with the Office of Regulatory Affairs

The monitor will report the following situations, should they occur, to the Office of Research Compliance and Regulatory Affairs:

- Persistent failure by the sponsor, investigator, or other member of the study team to follow the protocol;
- Persistent failure by the sponsor, investigator, or other member of the study team to follow GCP guidelines;

CLINICAL TRIAL PROTOCOL

Official Title	A Phase 2/3 Multicenter, Randomized, Double-masked, Parallel-group, Placebo-controlled Study to Investigate the Safety, Pharmacokinetics, Tolerability, and Efficacy of ALK-001 in Geographic Atrophy Secondary to Age-related Macular Degeneration
Brief Title	Phase 2/3 Study of ALK-001 in Geographic Atrophy (SAGA)
Sponsor	Alkeus Pharmaceuticals, Inc. 278 Elm St, Suite 229 Somerville, MA 02144 Direct Cell: +1.617.412.0644
Study Drug	ALK-001 (C20-D3-Retinyl Acetate, C20-D3-Vitamin A Acetate)
IND	108,353
Protocol Number	ALK001-P3001 (NCT Registration: TBD)
Monitor	Leonide Saad, Ph.D. 278 Elm St, Suite 229 Somerville, MA 02144 Direct: +1.617.412.0644
Compliance	This study will be conducted in accordance with standards of Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and all applicable federal and local regulations
Version:	v1.1 (02/01/2019)
Previous revisions:	v1.0 (05/01/2018)

Contents:

List of Abbreviations

ABCA4: ATP Binding Cassette Sub family A Member 4
A2E: N-retinylidene-N-retinylethanolamine (a representative RDDB)
AE: Adverse Event
ALK-001: C20-D3-retinyl acetate. The investigational drug assessed in this study.
ANOVA: Analysis of Variance
ALT: Alanine Aminotransferase
AMD: Age-related Macular Degeneration
AP: Alkaline Phosphatase
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
ATR: All-trans-retinal
BCVA: Best Corrected Visual Acuity
bHCG: Human Chorionic Gonadotropin
CBC: Complete Blood Count
CNV: Choroidal Neovascularization
CS: Clinically significant
CSR: Clinical Study Report
CRF: Case Report Form
ECG: Electrocardiogram
ERG: Electroretinogram
ETDRS: Early Treatment Diabetic Retinopathy Study
EVA: Electronic Visual Acuity
FAF: Fundus Autofluorescence
FDA: Food and Drug Administration
GA: Geographic Atrophy
GCP: Good Clinical Practice
HIPAA: Health Insurance Portability and Accountability Act
IND: Investigational New Drug
IOL: Intraocular Lens
IOP: Intraocular Pressure
IRB: Institutional Review Board
IReST: International Reading Speed Texts
IWRS: Interactive Web Response System
MedDRA: Medical Dictionary for Regulatory Activities
MP: Microperimetry
NCS: Non Clinically Significant
OCTA: OCT Angiography
PHI: Protected Health Information
PK: Pharmacokinetics
PRO: Patient Reported Outcome
RBP: Retinol Binding Protein
RDDB: Retinaldehyde Derived Dimerization Byproducts
RPD: Reticular Pseudodrusen
RPE: Retinal Pigment Epithelium
SAE: Serious Adverse Event
SD-OCT: Spectral Domain Optical Coherence Tomography
SMC: Safety Monitoring Committee
SOP: Standard Operating Procedures
ULN: Upper limit of normal
VFQ-25: Visual Function Questionnaire

1.1 STUDY SYNOPSIS

Official Title	A Phase 2/3 Multicenter, Randomized, Double-masked, Parallel-group, Placebo-controlled Study to Investigate the Safety, Pharmacokinetics, Tolerability, and Efficacy of ALK-001 in Geographic Atrophy Secondary to Age-related Macular Degeneration
Brief Title (Acronym)	Phase 2/3 Study of ALK-001 in Geographic Atrophy ("SAGA")
Protocol Number	ALK001-P3001
Version	v1.1
Phase	Phase 2/3
Methodology	This is a multicenter, randomized, double-masked, parallel-group, placebo-controlled study to assess the safety and efficacy of orally-administered ALK-001 (C20-D3-retinyl acetate) in subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Subjects, 60 years of age or older, who have been diagnosed with GA secondary to AMD, and who have no evidence of other conditions that might confound the diagnosis, progression, and measurement of GA lesions, will be invited to participate. Subjects must be deemed sufficiently healthy and likely to complete the full two-year duration of the study. For these subjects: - **at least one eye** (the "**study eye**") must have GA with (**i**) no concurrent or history of choroidal neovascularization (CNV), (**ii**) total GA lesions adding up to a total area between approximately 1.5 sqmm and 20 sqmm (approximately 0.5 to 9 Disc Areas), (**iii**) in the case of multifocal GA lesions, at least one contiguous GA lesion measuring approximately 1 sqmm or more, (**iv**) edges of GA lesions presenting with hyperautofluorescent patterns, and (**v**) an early treatment diabetic retinopathy study (ETDRS) best-corrected visual acuity (BCVA) of 33 letters or more (approx. 20/200). In case of foveal sparing, the shortest distance of GA borders to the center of the fovea must be less than approximately 250 µm. - the "**fellow eye**" (also called non-study eye), must present with at least one of the following: (**a**) reticular pseudodrusen (RPD), (**b**) intermediate AMD with at least one macular drusen greater than approximately 125 µm in diameter, (**c**) active or history of CNV, (**d**) geographic atrophy due to age-related macular degeneration, with or without a history of, or concurrent CNV. This study will enroll up to approximately n = 300 subjects. At the start of the screening period, subjects will be given a supply of placebo capsules to measure their compliance during a "run-in" period lasting 2 to 4 weeks. Subjects who match all eligibility criteria and are deemed adequately compliant during the run-in period, will be randomized to receive the study drug ALK-001 (n = 200) or placebo (n = 100) for a treatment period of 2 years. Following that initial treatment period, subjects will have the option to continue treatment in an optional open-label extension period (which will be fully described in future protocol amendments). Subjects who have participated in previous clinical trials may be eligible. Study participants, study team and sponsor staff in charge of day-to-day activities will be masked to the treatment group throughout the study. A Safety Monitoring Committee (SMC) will periodically review the safety data. A Statistical Analysis Plan (SAP) will detail analyses to be performed by independent statisticians.
Sample Size	With 300 subjects enrolled in the study and assuming that 80% of subjects are evaluable for the primary outcome measure, the study has an **80% power to detect, after 24 months of treatment, a 33% slowing in GA growth rate with a 2-tailed significance of 0.05** (assuming a standard deviation of 1.5 sqmm/year and an average progression of 1.8 sqmm/year in the control group)**.** As an exploratory measure and assuming that 35% of enrolled subjects have a fellow eye with active or history of CNV, the study has an **80% power to detect, after 24 months, a 75% reduction in incidental progression to CNV in the study eye** with a 1-tailed significance of 0.2 (Fisher's exact test).

Scientific Rationale	GA is an advanced form of AMD, characterized by well-demarcated atrophic lesions of the RPE and outer retinal layers. Symptoms of GA include uncorrectable central vision loss and other disturbances, along with the inability to see fine details, read, write, recognize faces, or drive. GA is currently untreatable, progressive, and leads to legal blindness. Retinaldehyde-derived dimerization byproducts (RDDB) are molecules that form non-enzymatically in the retina as byproducts of the visual cycle. RDDBs include molecules such as "A2E" and other vitamin A dimers, as well as their downstream degradation or combination byproducts. RDDBs form and gradually accumulate with age in the retina. These molecules are toxic to the retina and have been shown to cause, for example, chronic oxidative stress, inflammation, dysregulation of the complement, angiogenesis, and poisoning of the lysosomes, which are thought to contribute to the pathophysiology of AMD. Strategies to prevent RDDB formation have been explored as possible treatments of GA. To date, these strategies have relied on "modulating the visual cycle," by decreasing the vitamin A supply or its flow in the retina. Such approaches lead to adverse reactions such as night blindness, dark adaptation delays and chromatopsia, and might lead to long-term retinal toxicity. ALK-001 is a chemically-modified vitamin A whereby 3 hydrogen atoms have been selectively replaced by heavy hydrogen (also known as "deuterium"). Because deuterium and hydrogen are similar, ALK-001 preserves normal biological functions of vitamin A. Daily intake of ALK-001 leads to rapid replacement of the majority of vitamin A with a modified vitamin A that forms RDDB several folds slower, without affecting the visual cycle. As such, ALK-001 is not a visual cycle modulator. ALK-001 is a "clean tool" that can be used in clinical studies to measure the extent to which slowing RDDB formation retards the progression of GA and the incidence of CNV.
Study Duration	Approximately 3 years, including 8 months of enrollment, 24 months of treatment period, and 4 months of data analysis.
Study Center(s)	Multicenter.
Primary Objective	To assess the effects of ALK-001 on the growth rate of GA lesions after 24 months of treatment in patients with GA secondary to AMD.
Secondary Objectives	• To assess the safety and tolerability of ALK-001 in patients over 60 • To assess the pharmacokinetics of ALK-001 in patients over 60 • To assess the effects of ALK-001 on the growth of GA lesions after 12 months of treatment • To assess the effects of ALK-001 on the growth of GA lesions between 6 and 24 months of treatment • To assess the effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has CNV • To assess the effects of ALK-001 on visual function, including BCVA, LLVA, reading speed, questionnaires on quality of life and vision
Exploratory Objectives	• To assess the effects of ALK-001 on retinal anatomy (photoreceptors as measured by SD-OCT) • To assess the effects of ALK-001 on retinal function (measured by microperimetry) • Effects of ALK-001 on drusen characteristics • Effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has intermediate AMD • Effects of ALK-001 on the incidence of advanced AMD (CNV or GA), when the fellow eye has intermediate AMD • Effects of ALK-001 on the incidence of GA in eyes with CNV, when the fellow eye has GA • Distance of Preferred Retinal Locus (PRL) to foveal center and other fixation characteristics • Association between ALK-001 treatment effects and genetics • Association between ALK-001 treatment effects and complement
Number of Subjects	300 subjects, 60 years and older at the time of screening or randomization
Study Product, Dose, Route, Regimen	one capsule, containing ALK-001 or placebo, self-administered, once a day

Allocation of Subjects per Treatment Group	• ALK-001 (n = 200) • Placebo (n = 100)
Diagnostic code (ICD-10 classification)	Unilateral or bilateral advanced atrophic AMD with (**H35.31X4**) or without (**H35.31X3**) foveal involvement, secondary to non-exudative (dry) AMD (**H35.31X0**), where X = 1 (right eye) or X = 2 (left eye) *For the study eye:* *H35.3113 Nonexudative age-related macular degeneration, right eye, advanced atrophic without subfoveal involvement* *H35.3114 Nonexudative age-related macular degeneration, right eye, advanced atrophic with subfoveal involvement* *H35.3123 Nonexudative age-related macular degeneration, left eye, advanced atrophic without subfoveal involvement* *H35.3124 Nonexudative age-related macular degeneration, left eye, advanced atrophic with subfoveal involvement* *H35.3133 Nonexudative age-related macular degeneration, bilateral, advanced atrophic without subfoveal involvement* *H35.3134 Nonexudative age-related macular degeneration, bilateral, advanced atrophic with subfoveal involvement* *H35.3193 Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic without subfoveal involvement* *H35.3194 Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic with subfoveal involvement*
Reference Therapy	Placebo
SMC	An independent SMC will perform ongoing data reviews according to a SMC charter.
NCT Registration Number	TBD
Visit Schedules	Visit schedules will follow standard of care practices: study visits will take place every 6 months to check for AEs, compliance, clinical labs, and perform ocular testing and imaging. Short optional safety-only visits can take place every 3 months. See Events table in Section 1.2 for details.
Efficacy Outcome Measures	GA lesions as measured on FAF images and verified by SD-OCT, incidence of CNV, retinal anatomy by SD-OCT, visual function and quality of life questionnaires, reading speed, BCVA, low luminance VA, retinal sensitivity by fundus-tracking microperimetry (optional).
Safety Outcome Measures	Adverse events (AEs), serious AEs, clinical laboratory (biochemistry, hematology, lipids, glucose, vitamin A), physical exam, ocular exam, 12-lead ECG, vital signs, vision questionnaires.
Pharmacokinetic Parameters	Plasma vitamin A and ALK-001 metabolites
Statistical Methodology	*A detailed statistical analysis plan will be prepared prior to any efficacy unmasked data analysis. The following is provided for information only.* • Safety and tolerability will be summarized with descriptive statistics and individual patient narrative when necessary (SAEs, drop-out for safety, etc). • Pharmacokinetics will be analyzed with descriptive statistics. Percentage of deuterated vitamin A in plasma will be computed. • Efficacy will be assessed by comparing the following variables in subjects receiving ALK-001 vs. placebo: growth rate of GA lesions in the study eye, incidence of CNV in the study eye, changes in BCVA, changes in reading speed, changes in retinal sensitivity.

Inclusion Criteria	**All the following inclusion criteria must apply at screening, <u>except upon sponsor's approval</u>.** *<u>General</u> inclusion criteria:* 1. Male or female, 60 years and older. 2. Healthy as judged by principal investigator. 3. Has signed and dated the informed consent form. 4. Is able and willing to perform the study procedures. 5. Is able and willing to comply with the schedule of the study visits. 6. Is able and willing to self-administer the study drug. 7. Is able and willing to follow the instructions and comply with the avoidance of vitamin A supplements. 8. Is likely to complete the 2-year study as judged by principal investigator. *At least one eye, designated as the "<u>study eye</u>," must meet all the following inclusion criteria:* 9. Study eye displays GA lesion(s) measuring a total area between approximately 1.5 sqmm and 20 sqmm (0.5 to 9 Disc Areas), measured on fundus autofluorescence imaging (FAF), as confirmed by sponsor. 10. Study eye presents hyperautofluorescent patterns in the junctional zone of GA. 11. If GA lesions are multifocal in the study eye, one lesion at least must be approximately 1.00 sqmm or greater. 12. In case of foveal sparing in the study eye, the smallest distance between GA border and foveal center must be less than approximately 250 µm. 13. All GA lesions in the study eye must fit entirely within the 30-degree retinal imaging field centered on the fovea. 14. Study eye has BCVA of 33 letters (~20/200) or better. 15. Study eye has clear or adequate ocular media and pupillary dilation, including no allergy to dilating eyedrops, to permit good quality retinal imaging. *The non-study eye, designated as the "<u>fellow eye</u>," must meet the following inclusion criterion:* 16. Fellow eye presents with at least one of the following features: (**a**) reticular pseudodrusen (RPD), (**b**) intermediate AMD with at least one macular drusen greater than approximately 125 µm in diameter, (**c**) active or history of CNV, or (**d**) geographic atrophy with or without a history of, or concurrent CNV.

Exclusion Criteria	**All the following exclusion criteria must <u>not</u> apply, <u>except upon sponsor's approval</u>.** *<u>General</u> exclusion criteria:* 17. Active or historical medical condition (systemic or ophthalmic), which in the opinion of the principal investigator, may prevent performance of study procedures, compliance with the protocol, or continuous participation of the subject throughout the 2-year duration of study. 18. Currently taking or has taken medications associated with retinal toxicity, except for short durations as judged by principal investigator. 19. Is currently taking or is unwilling or unable to discontinue oral retinoids or medications that might affect absorption, metabolism, or function of vitamin A. 20. Has participated in any drug or device trial within 60 days of randomization. 21. Anticipates participating in any other drug or device trial over the next 2 years. 22. Is hypersensitive or allergic to fluorescein. 23. Has clinically-significant abnormal laboratory result(s) at screening, which in the opinion of the principal investigator, makes the patient unsuitable for study participation. 24. Has clinically-significant abnormal physical exam finding(s) at screening, which in the opinion of the principal investigator, makes the patient unsuitable for study participation. 25. Has active or historical, acute or chronic, liver disorder except when benign. 26. Has a clinically-significant cardiac abnormality, a clinically-significant abnormal ECG, or a marked prolongation of QTc at screening (>460 ms for male or >480 ms for female, approximately). 27. Female of childbearing potential, pregnant, lactating or positive serum pregnancy test at screening. *<u>Study eye</u> exclusion criteria:* 28. Study eye has historical or active CNV. 29. Study eye has refraction higher than 6 diopters (positive or negative) approximately, except if retinal imaging can be properly focused. 30. Study eye has GA thought or proven to be caused by any condition other than AMD. 31. Study eye has GA lesions expected to (i) expand larger than the imaging field of view, or (ii) merge with other retinal features (optic disc or peripapillary atrophy, other non-AMD atrophic lesions, etc.) during the 2 years of the study. 32. Subject, in the case of a systemic treatment, or study eye, in the case of a monocular treatment, has previously received treatment, surgery or procedure for GA or AMD, including clinical trials, except when there is documented evidence that the subject was receiving placebo or was part of a sham group. 33. Study eye has active or history of ocular disorder, which may confound assessment of the retina morphologically or functionally, as judged by principal investigator. 34. Study eye has uncontrolled elevated intraocular pressure, retinal detachment, RPE tear, recurring uveitis, retinal vein occlusion, diabetic retinopathy, diabetic macular edema. 35. Study eye has history of submacular surgery, any surgical intervention for AMD, vitrectomy, or device implantation (except IOL). 36. Study eye has received intravitreal injections or cataract surgery within 90 days of randomization. 37. Study eye is expected to require cataract, epiretinal membrane, or ocular surgery over the next 2 years as judged by principal investigator.

Study Procedures and Assessments	The Events table in Section 1.2 displays the timing of events and all evaluations for the study. See protocol for details on each evaluation as well as the specific order of procedures to follow, if any. The following lists all study evaluations: - Informed consent - Demographics and subject characteristics - Medical, surgical and ocular history - Collection of historical retinal images and records - Eligibility (Inclusion/Exclusion) criteria - Primary study eye - Ocular characteristics - Fundus features - Prior and concomitant medications - Adverse events (AE) and SAE - Check-up Phone calls - Study drug reconciliation - Vital signs - 12-lead electrocardiogram (ECG) - Physical exam or assessment - Ocular exam/evaluation - Best-Corrected Visual Acuity (BCVA) - Low luminance visual acuity (LLVA) - Reading speed (MNREAD and International Reading Speed Test IReST) - Questionnaires (may include Visual Function Questionnaire 25, Functional Reading Independence (FRI), or other visual function or quality of life questionnaires, as determined by sponsor) - Color fundus photograph (CFP) - Fluorescein Angiogram (FA) - Fundus Autofluorescence (FAF) - Spectral Domain Optical Coherence Tomography (SD-OCT) - Diagnosis and treatment of CNV (PI standard of care) - Microperimetry (where available) - Blood draw for clinical laboratory testing: Biochemistry, Hematology, Lipids, Pharmacokinetics - Blood draw for complement analysis - Blood draw or saliva sample for genotyping - Pregnancy test (serum) - Randomization - Drug dispensing

FAQ:

1. In general what kind of patients are eligible?

Patients 60 years old and above, with unilateral or bilateral GA. At least one eye must have pure GA (no history or concurrent CNV) and total GA lesions between 1.5 and 20 sqmm. The fellow eye can have either pure GA, concurrent or a history of CNV, CNV and concurrent GA, or intermediate AMD with at least one large macular drusen, or reticular pseudodrusen.

Patients should be deemed sufficiently healthy to complete the 24-month duration of the study. Comprehensive visits will be every 6 months with short optional safety visits every 3 months.

2. Can patients who previously entered clinical trials participate?

Yes.

3. What other non-AMD conditions or drugs can cause atrophic patches?

Several retinal diseases and dystrophies, systemic conditions, and drug-induced toxicity can cause atrophic patches that can be confused with AMD. Examples include Stargardt disease, pattern dystrophy, RPE tears, trauma, hemorrhage, drug-induced toxicity (hydroxychloroquine, didanosine, thioridazine, etc.), choroidal sclerosis, Bietti's crystalline dystrophy, etc.

Subjects thought to have GA secondary to any other condition than AMD will not be enrolled.

4. Can subjects take AREDS2 supplements during the study?

Yes, AREDS2 will be allowed and recommended for all patients, especially those with intermediate AMD in the fellow eye.

5. Can subjects take vitamin A-containing supplements or foods containing vitamin A or beta-carotene?

Subjects should avoid vitamin A or beta-carotene containing supplements, as well as food products containing overly high amounts of vitamin A such as liver or liver-based products/oils, giblets or other animal's internal organs, highly concentrated/processed fruit juices. All fruits and vegetables in their "natural," unprocessed form/concentration, are acceptable without restriction.

6. What happens to patients who develop CNV in the study eye? In the fellow eye?

Patients who develop CNV in the study eye continue the study and receive standard of care treatment as determined by each PI.

7. Can patients with history of or active CNV enroll?

Yes, as long as at least one eye has "pure GA" with no history of or active CNV.

8. Are subjects stratified?

No.

9. What are the expected outcomes for each eye based on their respective baseline?

Study Eye	Fellow Eye	Primary outcome	Secondary outcome
Pure GA	CNV	GA growth rate in study eye	Incidence of CNV in study eye (natural hx reports approx. 20% incidence at 24 months)
Pure GA	GA with or without CNV	GA growth rate in study eye	GA growth rate in fellow eye; Incidence of CNV in study eye (natural hx reports approx. 3-6% at 24 months)
Pure GA	Intermediate AMD with RPD or large macular drusen	GA growth rate in study eye	Incidence of advanced AMD (CNV or GA) in fellow eye (natural hx reports approx. ~20% incidence at 24 months)

1.2 EVENTS TABLE (INITIAL PERIOD)

Period	Screening and Run-In[15] Period - Baseline		Initial Treatment Period																
Study Months (m)	between approx. 2 and 4 weeks before day 1	Day 1 Randomization	Day 2-3 mo	3 mo	3-6 mo	6 mo	6-9 mo	9 mo	9-12 mo	12 mo	12-15 mo	15 mo	15-18 mo	18 mo	18-21 mo	21 mo	21-24 mo	24 mo End of Study	Early Termination[13]
Visit Window			monthly	See 11	monthly	See 11	monthly	See 11	monthly	See 11	monthly	See 11	monthly	See 11	monthly	See 11	monthly	See 11	
Visit (V) #	V01 Screening; Run-in[15] period starts	V02 Run-in period ends/ Randomization	Phone Follow-up	V03[12] (Optional)	Phone Follow-up	V04	Phone Follow-up	V05[12] (Optional)	Phone Follow-up	V06	Phone Follow-up	V07[12] (Optional)	Phone Follow-up	V08	Phone Follow-up	V09[12] (Optional)	Phone Follow-up	V10	ET (Early Termination)
Screening																			
Informed Consent	●																		
Demographics and Subject Characteristics	●																		
Medical, Surgical, and Ocular History	●																		
Collection of Historical Retinal Images and Records	●																		
Eligibility (Inclusion/Exclusion) Criteria	●	●																	
Primary Study Eye	●																		
Ocular Characteristics	O																		
Fundus Features[2]	●																		
General Health																			
Prior and Concomitant Medications	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Adverse Events (AE) and SAEs			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Check-up Phone Calls			●		●		●		●		●		●		●		●		
Study Drug Reconciliation		●		O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Vital signs	●	●		O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
12-Lead ECG	●							O[18]		●[18]		O[18]						●	O[13]
Physical Exam or Assessment[1]	C					ACI / RC				S / RC				ACI / RC				S / RC	O[13]
Ocular Exam/Evaluation[2]	●					ACI / RC				● RC				ACI / RC				● RC	O[13]
Quality of Life and Visual Function																			
Best-Corrected Visual Acuity (BCVA)[2]	●	O				●				●				●				●	O[13]
Low Luminance Visual Acuity (LLVA)[2]	●	O				●				●				●				●	O[13]
Reading Speed (IReST, MNREAD)[2]	●	O				●				●				●				●	O[13]
Questionnaires	●	●				O				●				O				●	O[13]
Ocular Imaging																			
Fundus Autofluorescence (FAF)[2]	●	O				● RC				● RC				● RC				● RC	O[13]
Spectral Domain OCT (SD-OCT)[2]	●					● RC				● RC				● RC				● RC	O[13]
Color Fundus Photograph (CFP)[2]	●					ACI / RC				ACI / RC				ACI / RC				ACI / RC	O[13]
Fluorescein Angiogram (FA)[2]	●					ACI / RC				ACI / RC				ACI / RC				● RC	ACI/RC
Diagnosis and Treatment of CNV																			
Diagnosis of CNV (PI SoC: either FA, OCT or OCTA)	SOC	SOC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC	ACI / RC
Treatment of CNV[16]	SOC	SOC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC	ACI / RC
Psychophysical function (Optional)																			
Microperimetry[2]	O	O				O				O				O				O	O[13]
Clinical Laboratory and Biological Samples (Central Labs)																			
Biochemistry[3]	●	O[12]		O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Hematology[4]	●	O[12]		O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Lipids[5]	●	O[12]		O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Glucose[14]	O	O[12]		O[12]		O		O[12]		O		O[12]		O		O[12]		O	O
Vitamin A and Pharmacokinetics (PK)[6]	●	O[12]		O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Complement[17]	See footnotes																	O	O[13]
Genotype[17]	See footnotes																		
Pregnancy Test[7]	O																		
Miscellaneous																			
Randomization		●																	
Drug Dispensing[9]	● Placebo	●		●		●		●		●		●		●		●		O	

● : Protocol Procedure O : Optional (Perform Upon Request) ACI/RC: Perform As Clinically Indicated or for Routine Care

1 *Comprehensive physical exam* (C) at V01, or simplified physical exam (S) at follow-up visits, when performed by PI or delegated personnel; *Limited physical assessment* if performed off-site by visiting nurse, where applicable.

2 Both eyes. Imaging performed according to manual of operation. For BCVA, EVA preferred, but ETDRS charts acceptable upon sponsor's approval. Microperimetry performed where available upon request by sponsor.

3 Biochemistry (CMP panel): Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine (with computed eGFR CKD-EPI), Calcium, Total Protein, Total Bilirubin, Albumin, Alkaline phosphatase, AST, ALT.

4 Hematology (with differential): WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBC, HGB, HCT, MCV, MCH, PLT.

5 Lipids: total cholesterol, triglycerides, HDL, LDL.

6 Collect approx. 10 mL of blood, extract plasma (2 vials of ~1.5 mL), store at below minus ~20°C (or temperature approved by sponsor) in provided glass vials, ship in bulk upon request by sponsor. Test performed by a central bioanalytical lab.

7 If PI cannot make a reasonable determination as to whether a subject is pregnant or of childbearing potential, PI may order a serum pregnancy test.

8 [Reserved]

9 Investigator may dispense the appropriate number of bottles to last until the next visit. At the end of V01, a bottle containing placebo is dispensed to check subject's proper compliance at V02. Refer to numeral 15.

10 [Reserved]

11 Visits shall preferably take place on their respective target dates, but can occur up to one week early. Visits should not occur after the target date. However, approvable exceptions to the visit window may be granted by sponsor upon reasonable request, if such exception would not be expected to influence data collection or continuous treatment of study subject.

12 PI may allow to skip one or several of the optional visits if PI does not have any safety concerns for a given subject based on review of ongoing AEs, and if subject is believed to be compliant with all study requirements. In case a visit is skipped, study team shall perform a phone call following the format of a "Phone Follow-up." In case of a skipped visit, study drug may be shipped directly to a subject and in-person assessments or procedures are skipped.

13 Perform optional procedures only if the early termination visit occurs more than 3 months following one of the long visits (in grey background): V04, V06, V08 and V10. Ask sponsor if unsure.

14 Random glucose may be measured if needed to confirm diabetic status

15 Run-In period: all screened subjects start receiving placebo for approximately 2 to 4 weeks to measure compliance to daily treatment. Subjects with greater than approximately 80% compliance during the run-in period will be randomized.

16 According to PI's standard of care.

17 Genotype and complement may be measured at any time during the study upon sponsor's request. Biological samples required for these tests can be stored at site and shipped in bulk upon request by sponsor.

18 ECG should be performed once either at V05, V06 (preferred) or V07 indifferently, per site preference.

1.3 EVENTS TABLE (OPTIONAL, OPEN LABEL EXTENSION PERIOD)

Period	Extension Period							
Study Months (m)	24-30 mo	30 mo	30-36 mo	36 mo	36-42 mo	42 mo	42-48 mo	48 mo end of study
Visit Window	bimonthly	±10 days[11]	bimonthly	±10 days[11]	bimonthly	±10 days[11]	bimonthly	±10 days[11]
Visit (V) #	**Phone Follow-up**	**V11**	**Phone Follow-up**	**V12**	**Phone Follow-up**	**V13**	**Phone Follow-up**	**V14**
Informed Consent	●							
General Health								
Concomitant Medications	●	●	●	●	●	●	●	●
Adverse Events (AE) and SAEs	●	●	●	●	●	●	●	●
Check-up phone calls	●		●		●		●	
Study Drug Reconciliation		●		●		●		●
Vital signs		●		●		●		●
12-Lead ECG								●
Physical Exam or Assessment		ACI / RC		ACI / RC		ACI / RC		S / RC
Ocular Exam / Evaluation		SOC		SOC		SOC		● RC
Quality of Life and Visual Function								
Best-Corrected Visual Acuity (BCVA)		O		●		O		●
Low Luminance Visual Acuity (LLVA)		O		●		O		●
Reading Speed (IReST, MNREAD)		O		●		O		●
Vision Questionnaires				●				●
Ocular Imaging								
Fundus Autofluorescence (FAF)		● RC		● RC		● RC		● RC
Spectral Domain OCT (SD-OCT)		SOC		SOC		SOC		SOC
Color Fundus Photograph (CFP)		SOC		SOC		SOC		SOC
Fluorescein Angiogram (FA)		SOC		SOC		SOC		SOC
Diagnosis and Treatment of CNV								
Diagnosis of CNV (PI SoC: either FA, OCT or OCTA)		SOC		SOC		SOC		SOC
Treatment of CNV		SOC		SOC		SOC		SOC
Psychophysical function								
Microperimetry		● RC		● RC		● RC		● RC
Clinical Laboratory (Central Lab)								
Biochemistry		●		●		●		●
Hematology		●		●		●		●
Lipids		●		●		●		●
Glucose		●		●		●		●
Vitamin A and Pharmacokinetics (PK)		●		●		●		●
Complement				**O**				**O**
Miscellaneous								
Drug Dispensing		●		●		●		

● : Protocol Procedure O : Optional ACI/RC: As Clinically Indicated or Routine Care

1.4 PROTOCOL AMENDMENTS

1.4.1 From Version 1.0 to Version 1.1

Section	Change
Throughout the document	Subjects must be randomized between 2 and 4 weeks from V01
Throughout the document	No vitamin A-related quiz or information required to continue participation in the study.
Throughout the document	Diagnosis and treatment of CNV performed according to PI's standard of care.
Events Table (1.2)	• Changes in visit window to reflect study drug supply • V03 is optional • 12-Lead ECG may be performed on either V05, V06 or V07 • Visual Acuity, Low Luminance Visual Acuity and Reading Speed are optional on V02. • Vision Questionnaires are performed once a year. • Color Fundus Photograph performed at V01, then as clinically-indicated. • Fluorescence Angiography is performed at V01 and V10, and as clinically-indicated. • Microperimetry is optional at V02
Throughout the document	Syntactic changes and addition of clarifying information
Throughout the document	Subjects no longer expected to fast prior to a visit
Throughout the document	Subjects allowed to take the study drug before a study visit.
Exploratory Outcome Measures (Section 1.6.2)	Measuring incidence of GA in eyes with CNV added as exploratory measure.
Visual Acuity	EVA preferred to measure visual acuity; ETDRS is acceptable.
Exclusion Criteria (1.8.2)	Study eye refraction may not be higher than 6 diopters (positive or negative) if retinal imaging can be properly focused, as determined by PI.
Exclusion Criteria (1.8.2)	Exclusion of uncontrolled elevated IOP.
Dispensing Study Drug (1.9.12.3)	Subject may be discharged 30 minutes after intake of 1st study drug.
Concomitant Medications (1.11)	Record use of retinoid medications up to 30 days prior to screening.
Concomitant Medications (1.11)	Subjects no longer prohibited from consuming saffron, curcumin, bilberry, "multivitamins for vision," resveratrol and CBD, however, the sponsor discourages their use.
Concomitant Medications (1.11)	Prescription eyedrops allowed for medical reason and according to approved label
Adverse Event and Serious Adverse Event Reporting (1.12.10 and 1.16.1)	Provided details on AE and SAE collection and reporting methods, especially with respect to progression of pre-existing condition(s) (GA or CNV), abnormal lab or ECG, and assessment of study drug causality

Laboratory testing	Random glucose optional throughout. Diabetic status preferably obtained during medical history.
Treatment Discontinuation (1.14.4)	Addition of objective, standard clinical trial criteria for discontinuing treatment in a subject
Visual questionnaire	VFQ-25 replaces VF-14

1.5 BACKGROUND INFORMATION

This document is the protocol for a multi-center phase 2/3 clinical trial to evaluate the effects of ALK-001, an investigational new drug (IND), on the progression of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Subjects enrolled in the study will be instructed to take one capsule per day containing ALK-001 or placebo for a period of 24 months. Up to approximately n = 300 subjects will be enrolled in the study. Subjects will be randomized 2:1 ALK-001:Placebo without stratification. At the end of the 24-month treatment period, subjects may be offered to enroll into an optional open-label, long-term extension, to evaluate the long-term effects of ALK-001.

Study visits will be scheduled to take place every ~6 months, with optional visits every ~3 months, essentially similar to US practices standard of care follow-up for GA patients. Every ~6 months, subjects will perform imaging and visual function tests, and undergo safety testing (including evaluation of adverse events, clinical lab tests, physical and/or ocular evaluation and management). At the optional 3-month visits, subjects will perform clinical lab tests.

To cover a clinically-representative population of patients with GA, only one (1) eye will be required to have GA ("study eye"), as GA lesion size will be measured to evaluate the primary endpoint. The fellow eye will present with at least one of the following features (**a**) GA, (**b**) intermediate AMD, characterized by a large macular drusen, or (**c**) historical or active choroidal neovascularization (CNV).

The area of GA will be measured using fundus autofluorescence (FAF) imaging, and will be characterized by well-demarcated dark lesions, and confirmed on optical coherence tomography (OCT) imaging. Subjects who present with or develop CNV during the study will be managed according to each site standard of care.

This study will be conducted according to US and international standards of Good Clinical Practice (GCP), applicable government regulations and institutional research policies and procedures. The sponsor of the study, Alkeus Pharmaceuticals, is dedicated to the subjects' rights and wellbeing and, prior to and during the course of the study, will ensure proper communication with and training of the investigators and study team, as well as monitoring of the study. An independent Safety Monitoring Committee (SMC) will monitor safety data throughout the trial.

1.5.1 Definitions: Investigator; PI; Sponsor

In this document, "investigator" or "study team" shall designate indifferently the entire clinical team, including the principal investigator (PI), sub-investigator(s), and the clinical research team (research coordinators, ophthalmic technicians, etc.) of each site participating in the study.

"Principal Investigator" or "PI" shall designate only the PI, i.e. the person signing form 1572. PI is responsible for the overall conduct of the clinical trial at his/her institution, and for the supervision and

oversight of adequately qualified and trained personnel who have been delegated protocol-related activities.

"Sponsor" shall designate the study sponsor, Alkeus Pharmaceuticals, and its affiliates or other representatives (including for example contract research organizations or other organizations acting on behalf of the sponsor).

"Study drug", "study medication" and "study treatment" shall be synonymous and designate the investigational treatment (drug or placebo) provided to study subjects.

Study "Subjects" or "participants" shall designate individuals who participate in the present study.

1.5.2 PI-only Procedures/Assessments

Whenever the protocol specifies that "PI" shall perform a procedure or assessment, this is to indicate that such procedure or assessment should only be performed by the PI, or by a sub-Investigator (sub-I), or personnel with a medical license that allows them to perform such task or procedure.

"PI-only procedures" include among others: final determination of inclusion/exclusion criteria, physical exam, eye exam, diagnosis and treatment of CNV, ECG review, assessment of clinical significance of clinical lab values, and assessment of AE (definitive diagnosis, association with study drug).

1.5.3 Resolution of Protocol Inconsistencies

In case a section of the protocol conflicts with another section resulting in a protocol inconsistency, investigator shall request clarifying instructions from sponsor. In case of a medical emergency, PI may use medical judgement and decide on how to interpret the protocol inconsistency. Inconsistencies and their resolution shall be documented in a Note to File and communicated to sponsor.

1.5.4 Background, Scientific Rationale and Proposed Trial

1.5.4.1 Background

The macula is located at the back of the eye in the center of the retina. When millions of cells in this light-sensitive, multilayer tissue deteriorate, central vision is lost along with the ability to read, write, drive and see colors. This so-called "macular degeneration" principally affects the elderly in a group of diseases called age-related macular degeneration (AMD). It is estimated that 8 million Americans are at risk for developing AMD.

In the United States, the combined prevalence of intermediate and advanced AMD increases with age from 7% (65-69 years old) to 24% (>80 years old) [1, 2]. While a treatment exists to prevent further progression of the wet form of AMD, called choroidal neovascularization (CNV), no treatment exists for dry-AMD, corresponding to over 80% of the AMD population, or for the millions of people at risk of developing AMD.

The long-term goal of this work is to develop an oral drug to prevent the development and slow the progression of AMD. The central hypothesis is that slowing vitamin A dimerization, an early event in the pathology of AMD, will slow the development and/or progression of the disease. In this protocol, we propose to evaluate the extent to which slowing the formation of toxic vitamin A dimers slows the progression of GA associated with AMD.

1.5.4.2 Scientific Rationale

AMD is characterized by an age-related degeneration of the retina. The root cause for this degeneration or the reason why some people develop AMD while others do not, is unknown. Over 20 years ago, it was hypothesized that the dimerization of vitamin A may be a significant contributor to the etiology of AMD. The eye indeed uses vitamin A as a cofactor to sense light, and a striking chemical signature of the aging and degenerating retina is the accumulation of vitamin A dimers in the retinal pigment epithelium (RPE) [3, 4] and the underlying Bruch's membrane [5]. In rodent models, high levels of vitamin A dimers correlate with poor retinal health [6-10], and a variety of mechanisms have been proposed by which vitamin A dimers may induce retinal toxicity [5, 11-50]. For example, the vitamin A dimer A2E has been shown to solubilize lipid membranes, inactivate lysosomes by increasing lysosomal pH, and accumulate in the negatively charged mitochondrial compartment causing mitochondrial toxicity. Once dimerized, the special orientation of the polyene chains makes dimers especially susceptible to oxidative degradation [33] leading to the generation of reactive aldehydes and epoxides that can go on to crosslink biomolecules [15, 51, 52]. Vitamin A dimers have been shown to up-regulate or directly bind to proteins involved in retinal function such as RPE65 [19], retinoic acid receptors [26], and cyclooxygenase-2 [32]. All of these mechanisms have been proposed as contributors to the development and progression of AMD.

Chronic activation of complement is thought to be paramount in the development and progression of AMD [53-56]. The exact triggers of complement activation are not known. Using *in vitro* and animal models, several groups have shown that dimers of vitamin A, such as A2E, directly activate complement [20, 30]. In addition, vitamin A dimers have been shown to be pro-angiogenic [23]. This suggests that the continuous formation of vitamin A dimers may directly provide an environment for chronic activation of complement and generation of vascular endothelial growth factor (VEGF) in the retina.

We have shown that long-term administration of ALK-001 to mouse models of retinal degeneration and in wild-type mice normalizes complement [57]. ALK-001 thus provides a powerful tool to chronically suppress the dimerization of vitamin A and examine the extent to which vitamin A dimers contribute to chronic activation of complement and to the development and progression of AMD.

In addition to AMD, dimers of vitamin A are found in other forms of retinal degenerations: for example genetic dystrophies known as Stargardt disease, vitelliform (or Best) macular degeneration (VMD), Sorsby's fundus dystrophy, malattia leventinese (Doyne honeycomb), and *ABCA4*-related cone-rod dystrophies all present with abnormal pigmentary changes in the retina indicative of vitamin A dimers [58-63]. These pigmentary changes, in almost all of the above conditions, precede vision loss. Based on the above observations, researchers have been feverishly developing strategies to reduce the formation of vitamin A dimers in hopes of preventing vision loss due to AMD and retinal dystrophies marked by the formation of vitamin A dimers.

For the purpose of reducing the formation of vitamin A dimers, researchers have observed that animals given vitamin A poor diets [64, 65], animals [66] and humans [67] with genetic defects in proteins involved in the use or the delivery of vitamin A to the photoreceptors (e.g. RPE65, LRAT, RBP4) all show little accumulation of these toxic vitamin A dimers. These observations led to the development of strategies to prevent the dimerization of vitamin A by partially depriving the photoreceptors of vitamin A. Photoreceptor deprivation is attempted by blocking the delivery of vitamin A to the eye or by inhibiting the vitamin A cycle. However, vitamin A stabilizes photoreceptor proteins, and when photoreceptors do not “contain” vitamin A, the retina undergoes degeneration. Indeed, many of the above conditions, where vitamin A delivery to the photoreceptors is impeded, such as retinitis pigmentosa, Leber congenital

amaurosis, or hereditary defects in RBP4, lead to retinal degeneration. Thus, despite avoiding the formation of vitamin A dimers, the retina may continue to degenerate due to empty photoreceptors. The absence of therapeutics that can slow the dimerization of vitamin A without depriving the photoreceptors has prevented elucidating the link between vitamin A dimerization and AMD.

In this protocol, we propose to evaluate a small molecule, ALK-001, that can prevent vitamin A dimerization without depriving photoreceptors of vitamin A. In mouse models of retinal degeneration, ALK-001 stops pathological changes of the retinal structure and slows declines in retinal function with age. Therefore, ALK-001 offers an exciting opportunity to clinically test the extent to which the dimerization of vitamin A contributes to AMD. If successful at preventing AMD, and because ALK-001 results from a "minor" chemical change of vitamin A (see below for details), ALK-001 could possibly become widely used in place of dietary vitamin A (vitamin A is exclusively found in food and most dietary vitamin A originates from man-made vitamin A placed in animal diet), similar to the way Iodine is supplemented in salt or vitamin D in milk. This could help prevent AMD in hundreds of millions of people worldwide, which would have a significant impact on public health.

1.5.4.3 Hypothesis

The major hypothesis behind this study is that impeding the formation of vitamin A dimers through daily of administration of ALK-001 will slow the progression of GA associated with AMD.

ALK-001 is an investigational drug that acts as a vitamin A replacement. ALK-001 is a chemically-modified vitamin A, with reduced propensity to dimerize. Because vitamin A dimers have been shown to trigger complement activation, we hypothesize that ALK-001 can also normalize overacting complement that leads to AMD, as was shown in preclinical work [68].

Importantly, ALK-001 is not expected to affect the visual cycle, and therefore will not result in visual side effects, such as blurred vision, night blindness, dark adaptation problems, as well as off-target effects that might result from the long-term impairment of the visual cycle. Because of its chemical structure, vitamin A where 3 hydrogens have been selectively replaced with 3 deuterium atoms (see Section 1.5.5), ALK-001 is expected to behave identically to vitamin A and have the same pharmacokinetics and ADME profile. As such, ALK-001 can be administered orally using formulations similar to those found in commercial vitamin A.

1.5.4.4 Proposed Trial: Phase 2/3 study to investigate the long-term safety, tolerability, pharmacokinetics and efficacy of ALK-001 in patients with GA secondary to AMD.

The proposed study aims to expand our understanding of the role of vitamin A dimers in the progression of forms of retinal degeneration characterized by the presence of vitamin A dimers in the retina. This study will evaluate the extent to which vitamin A dimers contribute to the progression of geographic atrophy secondary to age-related macular degeneration. The study has an 80% power, with a 2-tailed significance of 0.05, to detect a ~33% slowing in the growth rate of atrophic lesions measured between baseline and 24 months (primary outcome measure). Thirty-three percent slowing is approximately 1.5 to 2 times the average amount of slowing judged to be clinically-meaningful by retinal specialists caring for GA patients. The study eligibility criteria were designed to include a majority of patients with GA: if one eye must have "pure GA," the fellow eye may have GA, concurrent or history of CNV, or intermediate AMD with one large macular drusen. Estimating that approximately 35% of patients will have CNV in the fellow eye, the study has an 80% power to detect, at 24 months, a 75% reduction in the incidental progression to CNV in the study eye with a 1-tailed significance of 0.2 (Fisher's exact test).

1.5.5 Investigational Agent (ALK-001) and Regulatory History

The investigational drug ALK-001 (also known as C20-D3-vitamin A) is vitamin A, whereby 3 hydrogen atoms have been replaced with heavy hydrogen, also known as "Deuterium." Deuterium slows vitamin A's inherent ability to dimerize with itself, thereby preventing vitamin A dimerization.

ALK-001 nevertheless functions virtually identically to non-deuterated vitamin A except in its ability to dimerize: in an ongoing Phase 2 study in Stargardt disease, over 80% of the plasma's vitamin A was replaced with ALK-001's active form within weeks of daily oral administration of ALK-001. After 24 months of treatment, there were no reports of night blindness or delayed dark adaptation, nor any unexpected adverse reaction associated with the study drug, confirming that deuterated vitamin A can replace and act identically to non-deuterated vitamin A, in the eye and systemically.

1.5.5.1 Pharmacological mechanism of action

Previous work [69, 70] has demonstrated that the rate-limiting step of vitamin A dimerization is the non-enzymatic cleavage of a carbon-hydrogen (C-H) bond on the carbon number 20 of vitamin A. By replacing protium ("hydrogen") atoms of the C20 with heavier deuteriums (D), the C20 carbon-deuterium bonds become harder to cleave than the original C20-H bonds. This results in slowed dimerization, an effect called "kinetic isotope effect."

Deuterium is a naturally-occurring, stable, non-radioactive isotope of hydrogen. About 0.02% of hydrogen atoms are in the deuterium form. The tolerability of deuterium has been demonstrated in multiple studies dating back to the 1930s. For example in mice, replacement of up to 15% of all body water content with deuterated water, i.e. changing H_2O with D_2O, resulted in no toxicity or changes in the animals' health.

Deuterium is also called "heavy hydrogen" because its chemical properties are virtually identical to those of hydrogen, except in chemical reactions where carbon-hydrogens (or carbon-deuterium) bonds are broken. In the case of ALK-001, vitamin A was selectively deuterated at the carbon 20 position, a position known not to be chemically broken during normal vitamin A processing in the body, except when vitamin A forms its toxic dimers. As a result, ALK-001 is expected to behave identically to vitamin A, except for the fact that it should slow dimer formation.

In this clinical trial, a daily dose of ALK-001 contains over 100 times fewer deuterium atoms than deuterium molecules naturally-present in the average volume of drinking water consumed daily by an individual. Hence, deuterium atoms contained in ALK-001 are not expected to perturb the amount of deuterium naturally-contained in the body.

1.5.5.2 Expected safety and tolerability of ALK-001 in this study

A 24-month Phase 2 clinical trial is ongoing in subjects with Stargardt disease between 12 and 60 years old. As of September 2018, 50 subjects have completed a 12-month follow-up visit, 45 subjects have completed the 18-month follow-up visit, and 33 subjects have completed the 24-month visit. ALK-001 was well-tolerated with no unexpected adverse reaction, clinically-significant abnormal laboratory values, or any report of night vision changes or dark adaptation problems. In September 2018, the Data Monitoring Committee voted to continue the Stargardt study. The present GA study is expected to have the same safety and tolerability profile as the Stargardt study.

The following arguments further speak to the feasibility of the present study:

(1) ALK-001 has the same metabolism as vitamin A: ALK-001 is vitamin A where 3 hydrogen atoms have selectively been replaced with deuterium, to form deuterated vitamin A. Deuterium is a stable (non-radioactive) and naturally occurring (mostly as D_2O in sea water) isotope of hydrogen. Deuterium slows down reactions that involve the cleavage of a carbon-hydrogen bond. Because the carbon-hydrogen bonds that have been changed into carbon deuterium-bonds to form ALK-001 are not cleaved during vitamin A metabolism or usage [71], ALK-001 is expected to behave identically as normal, non-deuterated vitamin A in the body.
(2) ALK-001 behaves identically to vitamin A in the body: In the ongoing Phase 2, over 80% of plasma vitamin was replaced with deuterated vitamin A. No side effects typical of vitamin A deficiency were recorded. If ALK-001 could not carry out vitamin A's normal functions, one would have anticipated visual side effects (such as difficulty seeing in the dark or night, or difficulty adapting to wide changes in luminosity). In addition, several generations of mice have been given diets containing vitamin A only as ALK-001, and without naturally-occurring vitamin A, with no indication that ALK-001 behaves any differently from vitamin A.
(3) ALK-001 was well-tolerated in a study using the same dose and same duration of treatment proposed here: The tested dose has been assessed in a Phase 2 study in patients with Stargardt disease and found to be well-tolerated. Furthermore, higher levels of vitamin A have been previously given for up to 2 years in clinical trials, showing an acceptable tolerability profile [72].
(4) Deuterium atoms contained in ALK-001 will not cause biological changes: The number of deuterium atoms in a single dose of ALK-001 given in this study is over 100 times smaller than the number of deuterium molecules naturally found in the average volume of drinking water consumed daily.
(5) Unlike beta carotene, vitamin A acetate (ALK-001 parent compound) is not linked to lung cancer in smokers: Beta-carotene, the precursor of vitamin A, has been associated with increased risk of lung cancer in smokers or former smokers [73]. However, vitamin A itself is not associated with such increased risk [74] and as such, there is no need to prevent smokers or former smokers to enroll in this study. A systematic review on the topic can be found here [75].

1.5.6 Preclinical Data

A summary of preclinical data is presented in this section; comprehensive information is available in the investigator's brochure and in four peer-reviewed publications entitled "*C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt's disease*" [69], "*Deuterium enrichment of vitamin A at the C20 position slows the formation of detrimental vitamin A dimers in wild-type rodents*" [76], "*The retina rapidly incorporates ingested C20-D3-vitamin A in a swine model*" [16], and *"Rescue of the Stargardt phenotype in Abca4 knockout mice through inhibition of vitamin A dimerization"* [68]. These non-GLP studies were carried out at Columbia University under the direction of Ilyas Washington, and at Oxford University, under the direction of Robert MacLaren.

In the first publication [69], *Abca4*$^{-/-}$ mutant albino mice, the mouse model of human Stargardt disease, received diets containing either ALK-001 (the treated group) or vitamin A at its natural isotopic abundance ("non deuterated" vitamin A, the control group). The concentration of vitamin A dimers, lipofuscin and other biological markers indicative of ocular health in both groups were measured. Treated mice exhibited an 80% reduction in A2E, a 95% reduction in ATR dimers and a 70% decrease in fundus autofluorescence at three months of age. After six months of treatment, the treated group showed fewer lipofuscin granules as visualized qualitatively by electron microscopy, and at 12 months the mice showed improved retinal function as measured by ERG compared to the control group. Similar reduction (~60%) of A2E accumulation was also observed for mice reared on normal vitamin A diet for 2 months and then switched

to diets supplemented with ALK-001 for an additional month.

In work described in the second publication [76], *wild-type* rodents (mice and rats) received a diet containing either vitamin A (control group), ALK-001, or two inhibitors of A2E formation (Fenretinide [65] and TDH [77]). In this study, animals receiving ALK-001 had 45% less A2E compared to age-matched controls. Likewise, animals receiving Fenretinide or TDH had 58% and 40% less A2E respectively, relative to the control group. There was no statistically significant difference in the relative average decrease in A2E among all three inhibitors of A2E biosynthesis.

In the third publication [16], adult swine were fed a diet poor in vitamin A and rich in provitamin A carotenoids. Animals were given orally 3 mg of vitamin A per day, composed of ALK-001 (95%) and non-deuterated vitamin A (5%) mixed in olive oil and filled in a gelatin capsule similar to ALK-001 capsules. Five animals were sacrificed after 2 weeks and another five after 4 weeks. Plasma and tissues were collected at each sacrifice. The ratio of deuterated and non-deuterated vitamin A was determined by mass spectrometry. Results showed that about 85% and 95% of vitamin A was deuterated in the retina after 2 and 4 weeks respectively, indicating that steady state had been reached after 4 weeks. Further, provitamin A carotenoids (such as beta carotene) did not contribute to the vitamin A pool in the retina. Results also showed that the percent of deuterated vitamin A in the plasma closely mirrored that of the retina, indicating that plasma deuterated vitamin A percentage could be used as an indicator for the percentage of deuterated vitamin A in the retina.

In the fourth publication [68], wild-type and *Abca4*$^{-/-}$ pigmented mice were reared on the control vitamin A or treated with ALK-001. Treatment was started or crossed over back to the control diet at various time points. Results showed that replacing vitamin A with ALK-001 impedes the dimerization rate of vitamin A - by approximately fivefold for the vitamin A dimer A2E, and subsequent formation of lipofuscin and normalizes the aberrant transcription of complement genes without impairing retinal function. Phenotypic rescue by ALK-001 was also observed noninvasively by quantitative autofluorescence in as little as 3 months after the initiation of treatment, whereas upon interruption of treatment, the age-related increase in autofluorescence resumed. Results are in accord with research indicating the contributory role of vitamin A dimers in complement dysregulation.

Several generations of animals have been reared on diets containing vitamin A exclusively under the ALK-001 form (there was no “natural” vitamin A in the diet). There were no abnormalities that would suggest toxicity of ALK-001, nor was there any difference from animals reared on natural vitamin A: animals remained clean, sleek, well-groomed, alert and socially active, with good skin and mucosal color, and a tendency to explore the cage perimeter in all generations.

These preclinical results suggest that administration of ALK-001 may be a rational therapeutic approach to prevent vitamin A dimerization and slow the progression of retinal diseases.

1.5.7 **Clinical Data**

ALK-001 has been tested in two clinical trials: a Phase 1a, single center, open-label study (NCT02230228), designed to evaluate the safety and pharmacokinetics of various dose levels of ALK-001 administered daily for 4 weeks in healthy adult subjects, and a Phase 2, multi-center, double-masked, placebo-controlled study (NCT02402660), to assess the safety, tolerability, pharmacokinetics and effects of ALK-001 in subjects with Stargardt disease between the ages of 12 and 60 years old.

1.5.7.1 Efficacy

No human efficacy analyses have been performed to date. Please refer to preclinical data (1.5.6) for information on scientific rationale, hypothesis, mechanism of action, and efficacy data in mice.

1.5.7.2 Safety

NCT02230228 (completed) and NCT02402660 (ongoing) studies included the following safety evaluations: adverse events, clinical laboratory tests, 12-lead electrocardiograms, vital signs, physical examination. NCT02402660, which enrolled patients with Stargardt disease, further includes ocular tests, such as ocular exams, best-corrected visual acuity (EVA or ETDRS), self-reported vision questionnaire, fundus autofluorescence, OCT, microperimetry (optional), and dark adaptation testing (optional). Laboratory tests included the following:

- Biochemistry (Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Calcium, Total Protein, Bilirubin, Albumin, Alkaline phosphatase, AST, ALT).
- Hematology (WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBC, HGB, HCT, MCV, MCH, PLT).
- Lipid (NCT02402660 only): Triglycerides, total cholesterol, LDL, HDL

Subjects' age ranged from 13 to 62 across both studies. ALK-001 was shown to be well-tolerated in all subjects, at all tested doses, with no unexpected adverse reactions, consistent with the profile of vitamin A. In particular, there was no report of night vision or dark adaptation problems, no serious adverse events associated with the study drug, and no clinically-significant abnormal clinical laboratory tests. The dose proposed in this study is identical to one dose tested in NCT02230228 (for 4 weeks) and NCT02402660 (for up to 2 years). Based on all data collected to date, administration of ALK-001 in the proposed 2-year study in subjects with geographic atrophy, is expected to be well-tolerated.

1.5.7.3 Pharmacokinetics

Pharmacokinetics (PK) of ALK-001 has been evaluated in detail in NCT02230228 and NCT02402660. Please refer to the investigator's brochure for detailed information.

PK is measured by following ALK-001's metabolites in plasma. ALK-001 is a deuterated form of vitamin A *acetate*. Vitamin A *acetate* does not circulate in the blood. Instead, vitamin A acetate is metabolized during absorption into vitamin A alcohol (*retinol*), vitamin A esters (such as *retinyl palmitate*), and to a smaller extent *retinoic acid*. Levels of deuterated and non-deuterated retinol, retinyl palmitate and retinoic acid were measured regularly to assess compliance, as well as the replacement of vitamin A with deuterated vitamin A.

Because plasma vitamin A is comprised of retinol and retinyl esters, and because retinyl palmitate represents the majority of retinyl esters (approximately 65-75% [78, 79]), "vitamin A" was approximated as the sum of retinyl palmitate + retinol in plasma.

Total plasma vitamin A (the sums of each deuterated + non-deuterated metabolites of ALK-001) remained on average within known normal physiological ranges. There were no clinically-significant changes in the total amount of vitamin A in plasma after 24 months of treatment (based on interim analyses), indicating that ALK-001 replaces vitamin A with deuterated vitamin A but does not increase the body's total exposure to vitamin A.

Total retinoic acid. The total amount of retinoic acid in plasma, computed as the sum of deuterated and non-deuterated retinoic acid, remained on average within known normal physiological ranges after 24 months of treatment.

Percent deuterated vitamin A in plasma. The average percentage of deuterated vitamin A in plasma increased rapidly increased to reach 80% deuterated vitamin A after 4 weeks of daily treatment with ALK-001, and remained higher than 80% on average throughout the 24-month treatment duration.

1.5.8 Possible Risks and Benefits to Human Subjects

1.5.8.1 Possible Risks

- **Clinical laboratory results**: in an ongoing 2-year study assessing ALK-001 at a dose similar to the dose tested in this protocol, there were no reports of clinically-significant abnormal laboratory values, including for the enzyme levels and lipids listed below. Nonetheless, vitamin A has previously been associated with mild increases in the following blood parameters, which will be monitored for abnormalities and assessed for clinical significance (see 1.16):
    - *Enzyme levels:* ALT, AST and Alkaline Phosphatase.
    - *Lipids:* total cholesterol, triglycerides, HDL or LDL.
- **Side effects and toxicity:** Based on safety data acquired to date, adverse reactions due to ALK-001 at the proposed dose are expected to be rare in this 2-year study. The following side effects, associated with chronic vitamin A intake, may be reported by patients, although it is unlikely that such non-specific side effects would be associated with the study treatment in case they are reported within the first ~6 months of treatment.
    - Dermatological symptoms including dryness, desquamation or itching.
    - Alopecia, although this is not uncommon in the elderly.
    - Papilledema (optic disc swelling or fuzzy borders), with or without signs of headaches, intracranial hypertension (pseudotumor cerebri), transient visual obscurations (TVO), reports of a more noticeable or larger blind spot, transient nausea, stiff neck, dry skin or lips. Obese female subjects may be more sensitive to vitamin A.
    - Hepatomegaly, sometimes with splenomegaly
    - Other side effects related to chronic vitamin A intake may include: blurred vision, diplopia, anorexia, loss of appetite, nausea, fatigue, cheilitis, angular stomatitis, gingivitis, glossitis, conjunctivitis, peeling, epistaxis (nose bleed), pain of the bones, muscle stiffness, dysuria, exanthema, fever, vertigo, sleep disturbance, edema and swelling.
    - Vitamin A-related side effects or adverse reactions are known to resolve upon discontinuation of vitamin A treatment: therefore, if subjects present with non-tolerable adverse reactions, signs of toxicity, or symptoms which in the opinion of the investigator or sponsor may affect the health of the subjects, these subjects may be asked to temporarily interrupt the study treatment until resolution of the AE or decision to resume treatment (section 1.14.4).
- **Reproductive risks:** Female subjects of childbearing potential will not be allowed to enroll in this study, as there is a documented risk of birth defects in pregnant females due to chronic intake of vitamin A [80]. At screening, PI may decide to order a pregnancy test, which must be negative before a female subject can be randomized. There is no documented increased risk of birth defects for male subjects fathering a child while taking vitamin A. As such, there are no specific contraception requirements for male subjects.
- **Risk of medical procedures of the study:** The medical procedures involved in the study are all standard assessments performed as part of standard of care, and are of minimal risk.

1.5.8.2 Possible Benefits

- **Clinically-meaningful slowing of the growth rate of GA (Phase 3 section of protocol)**: The study is powered to detect a 33% slowing in the growth rate of atrophic lesions. A survey of retinal specialists indicates that on average a ~20% slowing in the growth rate of GA would be considered clinically meaningful. Here, the study duration of 24 months was chosen to be long enough to measure a clinically meaningful slowing of 33%, while adequately evaluating the long-term safety and tolerability of ALK-001. The dose level was chosen so that 80% of vitamin A would be replaced with deuterated vitamin A after the first four weeks of treatment. Eighty percent replacement is expected to be therapeutic.
- **Slowing of the progression from GA to CNV (Phase 2 exploratory section of protocol):** The study is further powered to detect a 75% slowing in the progression from GA to CNV in the study eye, when the fellow eye has CNV. When the fellow eye has CNV, natural history data indicate that the incidence of CNV in the GA eye is approximately 10% per year, or ~20% after the 24 months of this study. Because vitamin A dimers trigger angiogenesis, stopping the formation of vitamin A dimers could slow the progression to CNV of the GA eye.
- **Slowing of the progression from CNV to GA (Phase 2 exploratory section of protocol):** Studies have shown that after 24 months of anti-VEGF therapy, ~17% of eyes with CNV will develop GA. Stopping the formation of vitamin A dimers could slow the progression to GA in the CNV eye. This is an exploratory endpoint.
- **Slowing of visual acuity or reading speed loss:** Visual acuity is not an appropriate primary outcome measure in most geographic atrophy studies, because visual acuity only indicates the health of a small portion of the retina while the atrophy continues to degenerate in the retina. Nonetheless, visual acuity is known to progress at a rate of approximately 3-5 lost letters per year on the ETDRS chart, and the eye with better visual acuity is known to progress faster [81]. Subjects are expected to have on average ~20/40-20/100 visual acuity at baseline. Slowing the growth rate of atrophy, may also slow decreases in visual acuity or reading speed. Therefore, visual acuity and reading speed will be measured. In order to prioritize subjects whose visual acuity is likely to drop during the study, subjects with foveal sparing, will be required except upon approval by sponsor, to have borders of their GA lesion located at a distance to the foveal center of less than approximately 250 μm.

1.5.9 Significance of the proposed trial

There are no approved treatments for Geographic Atrophy, a condition that leads to legal blindness in almost all cases. Ongoing industry-sponsored clinical trials are investigating compounds injected intravitreally or subcutaneously and targeting the complement pathway. Results of clinical trials targeting the complement have been inconsistent. As such, there is a need to test an orally-delivered compound with a different mechanism of action.

An oral therapy is convenient for patients and physicians. In addition, because of its delivery mechanism and expected safety and tolerability, ALK-001 could later be tested in earlier stages of AMD, especially with intermediate AMD patients, as a prophylactic or disease-modifying agent to slow or prevent the progression of AMD to its advanced forms, GA or CNV.

To date, clinical data indicate that daily administration of ALK-001 is safe, well-tolerated, and replaces over 80% on average of vitamin A with deuterated vitamin A. In the present study, we aim to acquire safety, tolerability and pharmacokinetic data in patients aged 60 years old and over, and to measure the extent to which slowing vitamin A dimerization by ~4-fold slows the growth rate of GA lesions.

1.6 STUDY OBJECTIVES

1.6.1 Primary Objective and Primary Outcome Measure (Endpoint)

Primary objective:

- To assess the effects of ALK-001 on the growth rate of GA lesions after 24 months of treatment in patients with GA secondary to AMD.

Primary outcome measure (endpoint):

- Growth rate of the area of atrophic lesions between baseline and 24 months, as measured on fundus autofluorescence (FAF) imaging and verified by optical coherence tomography (OCT).

Methods of data analysis will be detailed in a Statistical Analysis Plan (SAP) prior to the performance of unmasked analyses. The SAP shall supersede this protocol in case of discrepancies with the SAP related to the choice of endpoints, power calculations, and statistical analyses. The SAP shall also be submitted to the regulatory agencies before any unmasked analyses are performed.

1.6.2 Secondary Objectives and Secondary Outcome Measures

Secondary objectives

- To assess the safety and tolerability of ALK-001 in patients over 60
- To assess the pharmacokinetics of ALK-001 in patients over 60
- To assess the effects of ALK-001 on the growth of GA lesions after 12 months of treatment
- To assess the effects of ALK-001 on the growth of GA lesions between 6 and 24 months of treatment
- To assess the effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has CNV
- To assess the effects of ALK-001 on visual function, including BCVA, LLVA, reading speed, questionnaires on quality of life and vision.

Secondary outcome measures (endpoints)

- Safety and tolerability assessed by frequency and severity of Adverse Events (AE) and Serious Adverse Events (SAE), as reported by patients
- Safety and tolerability assessed by frequency and severity of clinically-significant findings on 12-lead ECG, physical exam, ocular exams, retinal photographs, clinical laboratory tests, bioanalytical tests (vitamin A), BCVA
- Pharmacokinetics measured by the percentage of deuterated vitamin A in plasma
- Growth rate of GA lesions after 12 months as measured on FAF imaging and verified by OCT
- Growth rate of GA lesions between 6 and 24 months as measured on FAF imaging and verified by OCT
- Incidence of CNV in the study eye with GA, as assessed by PI using standard of care practice (including for example fluorescein angiography (FA), OCT, OCT angiography (OCTA), Color fundus photography, or combination)
- Changes in BCVA
- Changes in LLVA
- Changes in reading speed as measured by MNREAD and IREST

- Changes in quality of life, visual function or functional vision, as measured by Visual Function Questionnaire 25 (VFQ-25), Functional Reading Independence (FRI), or other vision, quality of life and AMD questionnaires.

1.6.3 Exploratory Objectives and Exploratory Outcome Measures (Research Only)

Exploratory objectives and exploratory outcomes

- To assess the effects of ALK-001 on retinal anatomy
  - Evaluation of photoreceptors and RPE layers on SD-OCT imaging. Specifically, evaluation of RPE, ellipsoid zone (EZ) band (also known as IS/OS junction layer) and outer nuclear layer (ONL)
- To assess the effects of ALK-001 on retinal function:
  - Changes in retinal sensitivity as measured by fundus-tracking microperimetry
- Effects of ALK-001 on drusen characteristics
  - Changes in drusen volume as measured by SD-OCT
- Effects of ALK-001 on the incidence of CNV in eyes with GA, when the fellow eye has intermediate AMD
  - Incidence of CNV in eyes with GA, as assessed by PI using standard of care (FA, OCT, CFP, OCTA or combination)
- Effects of ALK-001 on the incidence of advanced AMD (CNV or GA), when the fellow eye has intermediate AMD
  - Incidence of advanced AMD in the fellow eye, as assessed by PI
- Effects of ALK-001 on the incidence of GA in eyes with CNV, when the fellow eye has GA
  - Incidence of GA in eyes with CNV, as assessed by PI
- Distance of Preferred Retinal Locus (PRL) to foveal center and other fixation characteristics
  - Changes in fixation characteristics as measured by fundus-tracking microperimetry
- Association between ALK-001 treatment effects and genetics
  - Stratification of effect size by mutations on a panel of genes
- Association between ALK-001 treatment effects and complement
  - Stratification of effect size based on subject's complement function and complement blood levels

1.7 STUDY DESIGN AND RATIONALE

1.7.1 Overview of Trial Design

This is a randomized, double-masked, parallel-group, multicenter study evaluating the safety and efficacy of ALK-001 in subjects with GA secondary to AMD. Approximately 300 subjects who match all eligibility criteria will be randomized to receive either ALK-001 (n = 200) at 14 mg/day or placebo (n = 100) for 24 months in a 2:1 drug:placebo ratio. After 24 months of treatment, an optional open label extension is planned to determine the lowest chronic dose that can maintain approximately 80% of deuterated vitamin A in plasma.

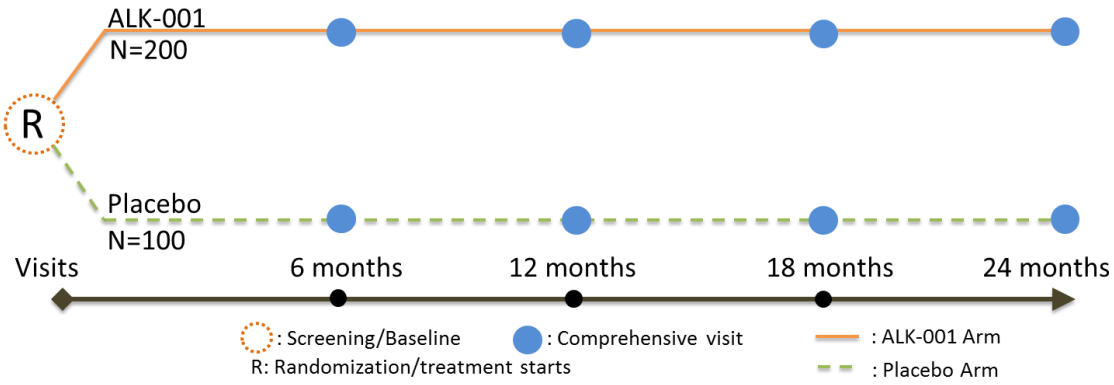
The expected total duration of the study from first patient first visit to last patient last visit, excluding the optional open label extension is 2 years and 9 months, which includes a total of up to 2 years of treatment with the study drug and 9 months of enrollment. Subjects, investigators and study team, and sponsor staff who may be in contact with investigators or subjects, will be masked for the duration of the study.

Safety and tolerability will be assessed by monitoring AEs, clinical laboratory tests, vital signs, ECG and physical examinations. The primary endpoint for assessment of efficacy is the growth rate of GA lesions

measured on FAF imaging and confirmed by OCT, between baseline and 24 months of treatment. Secondary efficacy endpoints include effects of ALK-001 on visual and ocular function and anatomy, as measured by questionnaires, BCVA, reading speed, and OCT. Exploratory outcomes measure include microperimetry and assessment of complement in the blood.

Protocol waivers or planned deviations may be allowed upon approval by sponsor and IRB when necessary. In certain cases, FDA review may be required, in which case such planned deviations or protocol waivers may be implemented only after receiving confirmation by sponsor that the FDA review period has been completed. Protocol waivers or deviations intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided that sponsor and IRB are subsequently notified, as required.

To the extent allowed in specific sections of this protocol, approvable exceptions may be granted by sponsor. Adherence to the study design requirements is essential and required for study conduct. Subject's health will be monitored through the end of the study. An independent Safety Monitoring Committee (SMC) will be commissioned to review unmasked safety data. All assessments will be performed according to the Events Table (1.2). A diagram of the study design and timelines is provided below.



1.7.2 Study Design Rationale

The study is designed to generate long-term safety and efficacy data of ALK-001 in subjects with GA secondary to AMD and otherwise deemed healthy to participate in the study.

1.7.2.1 Study Population

The study population comprises subjects 60 years old and over at the time of screening or at randomization, who are treatment-naïve to ALK-001 and have been diagnosed with geographic atrophy secondary to age-related macular degeneration in at least one eye. Subjects should be healthy otherwise, although benign conditions are acceptable if they are not likely to affect the subject's health, interact with the treatment, or confound the evaluation of safety, tolerability, or effects of ALK-001.

1.7.2.2 Dose Levels

A high percentage of deuterated vitamin A is recommended to demonstrate efficacy: ALK-001 is designed to replace normal vitamin A. The greater this replacement in the retina, the more efficacious ALK-001 will be at slowing the dimerization of vitamin A. Because measuring vitamin A in the retina is not directly accessible, an adult swine model has been used to demonstrate that the percentage of deuterated vitamin A in plasma mirrors that of the retina [16]. Thus, the percentage of deuterated vitamin A in plasma can be used as an indirect measure of the percentage of deuterated vitamin A in the retina.

Greater than 80% replacement of vitamin A with deuterated vitamin A is achievable: The percentage of *deuterated vitamin A* should preferably be over 80%, so that most vitamin A is in the deuterated form during the study. In mice models, ALK-001 prevented age-related declines in retinal function when as little as ≈ 80% of the vitamin pool was deuterated vitamin A (ALK-001's active metabolite) [70]. Eighty percent deuterated vitamin A resulted in greater than ≈ 4-fold reduction in the rate of dimerization. Phase 1 and Phase 2 clinical data indicate that once-daily intake of 14 mg of ALK-001 is sufficient to replace 80% of deuterated plasma vitamin A in humans after 4 weeks of treatment, with no major dietary restrictions (no liver, no vitamin A-containing supplements). Because a high percentage of deuterated vitamin A was achieved in plasma, it is unlikely that there would be a higher benefit from using a higher dose. As such, only one dose is being tested in this study.

At the dose level proposed in this study, the total intake of vitamin A (combining natural vitamin A from dietary sources + ALK-001 dose) is expected to be safe and well-tolerated for the 2-year treatment period: Daily intakes of vitamin A of ~100 mg (300,000 IU) for 1 year followed by ~50 mg (150,000 IU) during the second year were well-tolerated in a phase 3 cancer clinical trial enrolling close to 1,300 patients aged 23 to 83 years old [82] although some grade 3 and 4 toxic adverse events were observed. The degree of tolerability is usually higher in cancer trials. In another trial, daily dosing of 129 patients with sun-damaged skin for up to one year at doses up to ~25 mg (75,000 IU) of vitamin A has showed acceptable tolerability [72], while doses below ~8 mg (25,000 IU) have been shown to be relatively safe for decades [83]. Other trials testing vitamin A include a breast cancer trial testing ~100 mg per day (300,000 IU) for up to 2 years [84].

In an ongoing Phase 2 study, a daily administration of ALK-001 was well-tolerated, with no unexpected adverse reactions. It is important to note that vitamin A-related adverse reactions are known to resolve upon discontinuation. As such, if during the study any patient experiences signs or symptoms of hypervitaminosis A, which would place the patient at risk of continuing the study, such patient shall temporarily interrupt the study drug. See section 1.5.8.1 for details.

In the present study, we propose to assess the safety in patients older than 60 years old of daily intake of ALK-001 for a period of 24 months, and its efficacy on the growth rate of GA lesions. After 24 months, lower chronic doses may be assessed to determine the lowest dose that maintains ~80% deuterated vitamin A in plasma.

1.7.2.3 Treatment Groups

Subjects will be randomized to placebo or to ALK-001 at 14 mg/day.

Based on all mechanistic, preclinical and clinical information available to date, the chosen dose is likely to be therapeutic, as it will replace over 80% of vitamin A with deuterated vitamin A, which would be expected to slow the dimerization process over 2-fold in the retina. For percentages around 90% of replacement, dimerization is slowed 4-5 fold.

Considering the safety data to date, there is little scientific reason to explore a lower dose in the initial treatment period of 2 years, as it would increase the chance of missing a treatment benefit (type II error) without increasing the study safety in a meaningful way.

1.7.2.4 Route of delivery, frequency & time of dosage

Oral route preferred for ALK-001: The oral route is preferred as the retina is difficult to reach with topical formulations that might also be inconvenient (eyedrops, intravitreal injections). Vitamin A on the other hand can be taken orally and is naturally transported to the retina via retinol binding proteins (RBP) at physiologically relevant and controlled levels.

Once daily dosage preferred: Once daily dosing is recommended in this study based on pharmacokinetic data. Subjects will be advised to take their daily capsule at the same time each day, preferably at the time they take other medications if any.

1.7.2.5 Duration of Treatment

This study is designed to evaluate the safety and tolerability profile of ALK-001 in subjects over 60, and to determine the efficacy of ALK-001 on the progression of geographic atrophy.

The initial treatment period will end when the last subject completes the last scheduled visit.

A 2-year open label extension is planned to explore chronic maintenance dosing, as well as long term efficacy in case 2 years would not be sufficient to show an effect. Subjects who complete the initial treatment period may be offered to continue treatment, with a possible interruption between the first 2 years of treatment and the start of the open-label extension. Details of the extension period may be provided in future protocol amendments.

1.7.2.6 Study Control, Randomization and Masking

To prevent or reduce bias, a placebo will be used. This is particularly important as endpoints such as best-corrected visual acuity, reading speed, microperimetry, or assessments by the study team or reading center of RPE lesion atrophy, may be influenced with bias. Placebo will also be used to assess safety and establish the type, severity and frequency of adverse events associated with the drug.

Treatment masking will be in place to further reduce bias during data collection and analysis. Randomization will ensure there is no bias in the assignment of subjects to treatment groups, and to enhance the validity of statistical comparisons across treatment groups. No stratification will be used.

Investigators, subjects and all sponsor personnel having relevant contact with the study sites will remain masked to the treatment allocation for the duration of the study. The labels on the packaging of the study drug only indicate a random medication ID (eg: “GA2746”) and not the actual treatment assignment. All capsules will weigh, look, smell and taste the same unless specified otherwise by sponsor.

Unmasking of certain personnel when necessary for some data analyses, will require sponsor’s approval and will be clearly documented.

1.7.2.7 Safety Evaluations

Based upon vitamin A’s known safety and tolerability profile, possible AEs of interest have been identified and will be monitored during this study (see section 1.5.8.1). Safety data will be acquired by: 12-lead ECG, physical exam, ocular exams, retinal photographs, clinical laboratory tests, bioanalytical tests (vitamin A), BCVA.

To make sure that any potential for hypervitaminosis A is detected, *symptoms* such as headaches, nausea, dry lips, dry skin, *signs* such as papilledema (optic disc swelling), and clinically meaningful abnormalities

in clinical laboratories will be explored (see section 1.16.1.6). In addition, levels of retinol, retinoic acid, and retinyl esters will be measured periodically. In order to avoid study unmasking, such data will be reviewed by the SMC. See section below on pharmacokinetic evaluations.

Vitamin A-related adverse reactions are usually reversible upon discontinuation of the vitamin.

1.7.2.8 Pharmacokinetic Evaluations

Plasma will be collected to measure compliance and further assess the pharmacokinetic profile of ALK-001, how it might be influenced by dietary vitamin A intake, how it fluctuates over a 2-year period as liver stores are turned over, and how the percentage of deuterated vitamin A in the blood might be linked to the progression of GA.

Metabolites of vitamin A measured in this study: ALK-001 is expected to replace existing, non-deuterated vitamin A. Total vitamin A in the plasma will be approximated by the sum of retinol + retinyl palmitate. Levels of deuterated retinyl palmitate peak 4 hours following administration of one ALK-001 dose then rapidly return close to baseline levels 24 hours post-dosing. Levels of deuterated retinol increase more slowly to peak 8-12 hours following dosing and decrease more slowly over time. Retinoic acid, another vitamin A metabolite with direct function on vision, will be measured. The absolute levels and percentage deuteration of retinol, retinyl palmitate and retinoic acid will also be measured. Percentages are calculated as the ratio between the deuterated analyte and the total amount of each analyte. Total amounts of each analyte will be calculated as the sum of the deuterated and the non-deuterated analyte. Absolute levels above the upper limit of normal may not indicate toxicity in the absence of clinical signs or other clinically meaningful laboratory abnormalities.

Levels of each analyte are expected to remain below the following upper limit of normal, determined based on a review of the literature:

Analyte (total deuterated + non-deuterated)	**Approximate upper limit of normal**
Retinol	1,500 ng/mL
Retinyl palmitate (random)	5,000 ng/mL
Retinyl palmitate (12+ hour after dosing)	500 ng/mL
Retinyl palmitate (24+ hour after dosing)	200 ng/mL
Retinoic acid (random)	5 ng/mL

1.7.2.9 Efficacy Evaluations

Effects of ALK-001 on the progression of GA will be evaluated using fundus autofluorescence imaging. Although atrophic lesions can be readily measured using FAF imaging, OCT imaging will be used to confirm that the measured areas are indeed atrophic regions of the retina.

In addition, other measures of efficacy will be explored by measuring the following variables:

- Incidence of CNV,
- BCVA,
- Reading speed,
- Visual questionnaires, and
- Microperimetry (at sites where available).

1.7.2.10 Complement and Genotype (Optional)

This section is optional and may be revised. We propose to explore the association between each subject's response to ALK-001 and their complement status, as determined by *genetic polymorphisms (SNPs*, *serum levels*, and complement *function (*synonym of *"activity"*. Studying the complement in this study is relevant because vitamin A dimers are known to activate the complement cascade [20, 30]. Studies have shown that inhibiting dimerization in mouse leads to normalization of the transcription of genes involved in the complement [85].

The complement system comprises approximately 20 proteins synthesized by the liver and the RPE [86]. AMD risk is associated with DNA variants for the genes encoding for complement system proteins. For example, complement factor H (CFH) is strongly associated with AMD [53-56], with a single common variant explaining ~43% of AMD risk in older adults. Common genetic variants in complement component C3, Factor B, C2, and Factor I also confer a risk for the disease [87]. In contrast, certain mutations spanning CFH confer protection from developing AMD [88, 89]. Genetic testing can give information about the risk of developing AMD, but to date there have been no solid associations between genetic mutations and severity of geographic atrophy progression, or response to therapeutic intervention [90-92]. To address this shortcoming, this study will carry out genetic testing and quantification of serum complement proteins, and in addition will test the actual function (see table below) of the complement system in each patient, as genetic variants may result in differences in complement function even in absence of gene expression differences. As complement function is constant over time [93, 94], and complement is expected to function similarly in the retina, complement function in the plasma will be measured using the commercial CH50 and AH50 tests.

We suspect that vitamin A dimers, which form on the surface of the phospholipids of the disk membranes, modify disk membranes in ways that activate complement. Such complement activation caused by vitamin A dimer-modified disk membranes would explain data linking vitamin A dimers to complement. Such a scenario would also predict that patients whose complement system reacts more strongly to dimer-altered disk membranes would most benefit from preventing such alteration through administration of ALK-001. We thus plan to evaluate complement status as a means to predict the extent to which patients may benefit from ALK-001. We will search for a correlation between complement serum levels and/or genetic polymorphisms of approximately 20 AMD-associated genes, and/or, complement function with treatment effects measured as GA growth rates.

Accordingly, we may collect blood or saliva samples from participants in order to test the following (list may be revised in a separate document without amending this protocol):

(1) Complement *function* will be measured using two commercial assays:

Test Name	Notes	Range	Ref.
Complement, Total, function (CH50)	Measures the ability of the membrane attack complex to form and lyse altered liposomes decorated with foreign dinitrophenyl groups.	30-75 U/mL	[95]
Complement, Alternate (AH50)	Activates serum then quantifies formation of the C5b-9, membrane attack complex, via the alternative pathway	>46%	[96]

(2) Complement *serum levels* of C3d, Ba, C3a, C5a, SC5b-9, C3, C4, factor B, factor H and factor D will be quantified.

(3) *Complement genetic polymorphisms (SNPs)* of 20 genes associated with AMD will be tested by a CLIA-certified lab. The genes include: ABCA4, C2, C3, CFB, CFH, CFI, CNGB3, CST3,

CX3CR1, EFEMP1, ELOVL4, ERCC6, FBLN5, HMCN1, HTRA1, PRPH2, RAX2, RLBP1, RPGR, TLR4, as well as ARMS2 individually. This list may be amended by sponsor.

We may compare 1) Complement *function;* and/or *2* Complement *serum levels and 3 Complement genetic polymorphisms (SNPs* with rates of GA growth as determined by FAF, in order to determine the extent to which any of these variables is predictive of those AMD patients most likely to benefit from ALK-001.

1.7.2.11 Avoidance of vitamin A supplements and liver products during the trial

Because ALK-001 replaces vitamin A, any overly high intake of dietary vitamin A will reduce the activity of the drug. Study participants should avoid consumption of vitamin supplements containing vitamin A or beta-carotene, and liver-based products (liver, liver oil, liver sausage, etc.). Consumption of fruits and vegetables is not restricted. See section 1.11.2 for details.

1.8 SUBJECT SELECTION

1.8.1 Inclusion Criteria

A prospective subject will be eligible if he/she meets **all** the following inclusion criteria at screening or at randomization (as applicable), except upon sponsor's approval which shall be documented:

General inclusion criteria:

1. Male or female, 60 years and older.
2. Healthy as judged by principal investigator.
3. Has signed and dated the informed consent form.
4. Is able and willing to perform the study procedures.
5. Is able and willing to comply with the schedule of the study visits.
6. Is able and willing to self-administer the study drug.
7. Is able and willing to follow the instructions and comply with the avoidance of vitamin A supplements.
8. Is likely to complete the 2-year study as judged by principal investigator.

At least one eye, designated as the "study eye," must meet all the following inclusion criteria:

9. Study eye displays GA lesion(s) measuring a total area between approximately 1.5 sqmm and 20 sqmm (between ~0.5 and ~9 Disc Areas), measured on fundus autofluorescence imaging (FAF), as confirmed by sponsor.
10. Study eye presents hyperautofluorescent patterns in the junctional zone of GA.
11. If GA lesions are multifocal in the study eye, one lesion at least must be approximately 1.00 sqmm or greater.
12. In case of foveal sparing in the study eye, the smallest distance between GA border and foveal center must be less than approximately 250 µm.
13. All GA lesions in the study eye must fit entirely within the 30-degree retinal imaging field centered on the fovea.
14. Study eye has BCVA of 33 letters (~20/200) or better.
15. Study eye has clear or adequate ocular media and pupillary dilation, including no allergy to dilating eyedrops, to permit good quality retinal imaging.

The non-study eye, designated as the "fellow eye," must meet the following inclusion criterion:

16. Fellow eye presents with at least one of the following features:

(**a**) reticular pseudodrusen (RPD),
(**b**) intermediate AMD with at least one macular drusen greater than approximately 125 μm in diameter,
(**c**) active or history of CNV, or
(**d**) geographic atrophy with or without a history of, or concurrent CNV.

1.8.2 Exclusion Criteria

A prospective subject will **not** be eligible if **any** of the following criteria apply at screening or at randomization (as applicable), except upon sponsor's approval, which shall be documented:

General exclusion criteria:

17. Active or historical medical condition (systemic or ophthalmic), which in the opinion of the principal investigator, may prevent performance of study procedures, compliance with the protocol, or continuous participation of the subject throughout the 2-year duration of study.
18. Currently taking or has taken medications associated with retinal toxicity, except for short durations as judged by principal investigator.
19. Is currently taking and is unwilling or unable to discontinue oral retinoids or medications that might affect absorption, metabolism, or function of vitamin A.
20. Has participated in any drug or device trial within 60 days of randomization.
21. Anticipates participating in any other drug or device trial over the next 2 years.
22. Is hypersensitive or allergic to fluorescein.
23. Has clinically-significant abnormal laboratory result(s) at screening, which in the opinion of the principal investigator, makes the patient unsuitable for study participation.
24. Has clinically-significant abnormal physical exam finding(s) at screening, which in the opinion of the principal investigator, makes the patient unsuitable for study participation.
25. Has active or historical, acute or chronic, liver disorder except when benign.
26. Has a clinically-significant cardiac abnormality, a clinically-significant abnormal ECG, or a marked prolongation of QTc at screening (>460 ms for male or >480 ms for female, approximately).
27. Female of childbearing potential, pregnant, lactating or positive serum pregnancy test at screening.

Study eye exclusion criteria:

28. Study eye has historical or active CNV.
29. Study eye has refraction higher than 6 diopters (positive or negative) approximately, except if retinal imaging can be properly focused.
30. Study eye has GA thought or proven to be caused by any condition other than AMD.
31. Study eye has GA lesions expected to (i) expand larger than the imaging field of view, or (ii) merge with other retinal features (optic disc or peripapillary atrophy, other non-AMD atrophic lesions, etc.) during the 2 years of the study.
32. Subject, in the case of a systemic treatment, or study eye, in the case of a monocular treatment, has previously received treatment, surgery or procedure for GA or AMD, including clinical trials, except when there is documented evidence that the subject was receiving placebo or was part of a sham group.
33. Study eye has active or history of ocular disorder, which may confound assessment of the retina morphologically or functionally, as judged by principal investigator.
34. Study eye has uncontrolled elevated intraocular pressure, retinal detachment, RPE tear, recurring uveitis, retinal vein occlusion, diabetic retinopathy, diabetic macular edema.

35. Study eye has history of submacular surgery, any surgical intervention for AMD, vitrectomy, or device implantation (except IOL).
36. Study eye has received intravitreal injections or cataract surgery within 90 days of randomization.
37. Study eye is expected to require cataract, epiretinal membrane, or ocular surgery over the next 2 years as judged by principal investigator.

NOTE: PI shall make the final determination regarding all eligibility criteria.

1.8.3 Study Requirements, Restrictions and Instructions for Subjects

Investigator should enroll participants they believe will follow the study requirements and be likely to complete the 24-month treatment period. Investigator shall discuss with prospective and enrolled subjects about the importance of the study requirements outlined below. Subjects must be willing and able to continuously adhere to the study requirements throughout the duration of the study. Non-compliant subjects may be withdrawn from and discontinue the study, and have to interrupt the study treatment. Details about each of the below requirement are found in the corresponding section.

1. **Adherence to visit schedule**: subjects will be informed about the schedule of all future visits and should ensure they have the time to participate in the 24-month study, and they are able to travel to/from the sites. Missed visits may result in withdrawal.
2. **Study procedures**: subjects should be informed of which study procedures will be performed.
3. **Compliance with study drug intake**: subjects should be informed before the study, and reminded during the study, to take the drug daily for 24 months, preferably at the same time every day and at the same time they take their other medications, unless prescribed otherwise by the investigator.
4. **Subjects must not consume dietary supplements containing vitamin A, liver-based products, or foods known to contain excessive amounts of vitamin A** (section 1.11.2).
5. **Subjects should not take any medications prohibited under this protocol,** except when medically indicated, for the duration of the study (section 1.11.3).
6. **Subjects must not enter into any other investigational drug or device** clinical study, unless deemed medically necessary by the PI and sponsor.
7. **Subjects must not become pregnant during the study.**

1.8.4 Exemptions to Entry Criteria

Subjects must be compliant with all inclusion and exclusion criteria, unless an approvable exception is granted by sponsor according to section 1.17.12.

1.9 STUDY DRUG ADMINISTRATION AND MANAGEMENT

1.9.1 Treatment Groups

Subjects will be considered "enrolled" when they are determined to have met all eligibility criteria **and** after they are randomized to a treatment group. Subjects will be randomized 2:1 to ALK-001 or placebo. The treatment period will last 24 months and subjects and investigator will be masked to treatment group.

1.9.2 Timing of study drug intake

a) Subjects will be instructed to take one capsule per day, by mouth, at a time of their preference, preferably at the same time they take their other daily medications.
b) Subjects will be instructed to take the study drug at approximately the same time each day.

c) Time of usual study drug intake, duration elapsed since last study drug intake (at the time blood samples are collected during follow-up visits), and whether the capsule is taken before, after or during a meal should be recorded.

1.9.3 Missed Dose

a) Subjects should avoid missed doses.
b) If a subject forgets to take a dose, they should take the missed dose as soon as they remember it, even if that means taking 2 doses on the same day.
c) Subjects should not take more than 2 capsules in one day.

1.9.4 Method of Assigning Subjects to Treatment Groups

1.9.4.1 Randomization

Only after receiving authorization to do so by the sponsor, investigator will randomize subjects who have been confirmed to meet all entry criteria at the beginning of the run-in period and since then have not had any clinically-significant changes in health, which in the opinion of the principal investigator, would make the subject unsuitable to continue participation in the study. Randomization consists in assigning a medication ID to a subject and dispensing the study drug, usually on the same day. Subjects are allocated treatment by block.

1.9.4.2 *Errors in Medication ID assignment*

If a subject is assigned a medication ID in error (except for placebo during run-in period and has not started treatment, the error shall immediately be corrected and documented, so that the subject receives the medication he/she was supposed to receive.

If a subject has already been dispensed and has already taken one capsule of the wrong medication ID, the drug dispensed medication ID shall now prevail and should replace the medication ID originally intended to be dispensed.

No two subjects shall be assigned the same medication ID (except during run-in period, and if such dispensing error has been made, the subject receiving the wrong medication shall be informed to immediately stop taking the wrongly provided medication, return all provided medication, and start receiving the proper medication. Randomization date shall be adjusted to the date at which the subject started the proper medication. A note should be added to the source documents to explain the discrepancy. If this dispensing error results in insufficient study drug available for a given subject, refer to section 1.9.8.2.

1.9.4.3 Randomization Process

A randomization list is used to select which medication ID to dispense to each subject. The investigator must pick the next medication ID available at the clinical site, by following the order on the masked randomization list that will be distributed at the start of the trial, or by using an Interactive Web Response System (IWRS for randomization. Sponsor will be responsible for ensuring that study drug supplies are delivered to each site. Investigators should inform sponsor in advance of subjects' scheduled randomization visits, so that sufficient drug supply is already at the site on the scheduled day of randomization.

Once randomized, subjects will immediately receive the applicable study drug either through PI or designated personnel, through site pharmacy, or directly by mail. If received by mail, subjects will be requested to confirm receipt, which shall be documented.

1.9.4.4 *Randomization code, randomization list (or schedule):*

A randomization code, used to prepare the randomization list, will first be prepared by the sponsor. The code will be programmed to be reproducible if the need arises. Once approved, this code will be tested by sponsor to generate a dummy randomization list for quality control. Once the code has been verified to meet protocol requirements, an unmasked vendor/consultant designated by the sponsor will generate the final randomization lists (masked and unmasked. The *unmasked* randomization list will be accessible to select persons only (SMC members, unmasked statistician(s, label printing company, packaging company, other unmasked organizations. The investigator and the sponsor will receive a copy of the *masked* randomization list which will contain the sequence of medication IDs, but not the actual treatment allocation nor any information about blocks order or size. Any further instructions for randomization will be provided separately.

1.9.5 **Treatment Allocation**

To assure even treatment balance and minimization of bias, subject allocation to treatment group will be determined using random permuted block randomization, without stratification. The following tables summarize the expected enrollment:

Treatment Group	Total
Placebo	100
ALK-001 14 mg/day	200
Total	300

1.9.6 **Dose Modification or Interruption**

Except when approved by sponsor or as permitted in other sections of this protocol, modifications of the study drug dosage are prohibited, including if subject has received the incorrect drug dose by mistake. If study drug dosing must be interrupted (see 1.14.4), the subject may be discontinued from the study after discussions with the sponsor (see 1.14.6).

1.9.7 **Masking / Unmasking**

1.9.7.1 Masking to Treatment Assignment

Subjects, site personnel, pharmacy personnel, monitors and sponsors will remain masked to the treatment assignments throughout the study, except as provided in 1.9.7.3. The below list provides a list of personnel involved in the study and whether they should be masked to treatment ("M" or unmasked to treatment ("U". If necessary for the conduct of the study, this list might be amended by the sponsor and if so, will be documented in the regulatory binder. The list of persons authorized to receive unmasked data/treatment code may be amended from time to time by the sponsor.

	Treatment assignment	Bioanalytical data
Sponsor personnel with direct or indirect access to clinical data (Coordinating Personnel)	M	Available, masked to treatment and subject ID
Site study team (including PI, sub-I, coordinator)	M	Available, masked to treatment and subject ID
Site pharmacy (if applicable)	M	-
Monitor	M	Available, masked to treatment and subject ID
Central Lab	M	-
Reading Center (Retinal Imaging)	M	-
Bioanalytical laboratory	M	U
Study drug supply management designee	U	-
Quality assurance person / Unmasked monitor	U	U
SMC	U	U
Statistician preparing unmasked analyses	U	U
Designees preparing randomization list	U	-

- does not have access to data
M masked to treatment
U unmasked to treatment

1.9.7.2 Masking to PK data

For each subject in the trial, the bioanalytical lab or an unmasked person may generate and assign a random subject PK ID to each subject (which will be different from the medication ID or the actual subject ID. This is to mask the subject ID from the clinical team and sponsor, but still be able to provide individual data to masked personnel.

Full, identifiable results containing subject IDs, site, treatment allocation, or blood collection date can only be provided to authorized personnel, which shall include at least the SMC, statisticians and unmasked personnel designated by the sponsor.

Sponsor and investigators should be allowed to review PK data on an-ongoing basis as long as such data does not enable treatment unmasking. The bioanalytical lab or a designated unmasked person will be in charge of reviewing the PK data and/or providing a redacted version to the sponsor and investigators.

For that, all pharmacokinetic data and treatment assignment (active dose vs. placebo will be made available, but will not contain the subject's identity (i.e. subject ID number, medication ID, nor the dates of visit, specific site, or any other information that could result in unmasking or partial unmasking of the treatment allocation. The table should contain the masked subject PK ID. Furthermore, datasets shall be provided only in bulk following the randomization block, or as determined appropriate by the statistician. Special precautions should be taken after subjects are withdrawn from the study, or for subjects with missed data/visits to avoid unmasking. Such precautions shall be put in place by the designated person providing the data to the sponsor and investigators.

Hypothetical example of bioanalytical table that can be sent to masked personnel:

Subject ID	Subject PK ID	Collection Date	Collection Time	Retinol Conc. (ng/mL)	Retinol-d_3 Conc. (ng/mL)	Visit
[redacted]	001	[redacted]	[redacted]	380	0	V01
	001			80	400	V03
	001			40	450	V04
	002			520	0	V01
	002			80	450	V03
	002			35	500	V04

1.9.7.3 Unmasking of individual study subjects in case of medical emergency

The code linking treatment to medication ID will be maintained (i by the labeling company, (ii by the unmasked statistician(s, to allow the investigator to break the masking for an individual subject solely in the case of a medical emergency or necessity.

Unmasking: **Code breaks must occur only when specific knowledge of the treatment group (treatment or placebo) would dictate the treatment or course of action to follow to manage the subject's medical emergency or necessity**.

In the event a code break must occur, the investigator will first contact the sponsor prior to unmasking (contact details found on cover page. For life-threatening serious adverse event only, and if the investigator has been unsuccessful in contacting the sponsor, the investigator may proceed with unmasking the subject without first notifying the sponsor by following unmasking instructions provided in the study binder. The investigator must then notify the sponsor within 24 hours of breaking the code. Information pertaining to all circumstances that resulted in unmasking, such as reason, date and time, shall be clearly recorded in the subject's source documents. In addition, the sponsor may also, for matters relating to health risk concerns, unmask individual subjects at any time.

After unmasking: After unmasking of a particular subject, the subject should permanently interrupt the treatment and be withdrawn, unless instructed otherwise by sponsor. In addition, the nature of the treatment (treatment or placebo should be stored in a sealed, labeled and signed envelope so that the subject, study site or sponsor stay masked to the treatment until the end of the study. The investigator should not reveal the nature of the treatment to the subject, the sponsor, or other study team members until after the end of the study.

Unintentional unmasking: In case of unintentional unmasking by subject or study team, the date and reason must be documented and sponsor informed promptly. Sponsor will decide whether subject should be kept in the trial, re-randomized, or withdrawn.

1.9.8 Dose Abuse, Lost Medication or medication shortage

1.9.8.1 Dose abuse

Subjects will be discouraged to take more than one capsule per day, except in case of a missed dose. Because only the percentage of deuterated vitamin A, rather than the absolute values of vitamin A is believed to affect efficacy, there is no expected benefit in taking more than one capsule per day. Taking more than one capsule per day may increase the chance of adverse reactions and lead to subject withdrawal for non-compliance with study instructions.

1.9.8.2 Lost medication or medication shortage

In the event a subject loses a medication packaging, a replacement may be provided if available. To avoid abuse, subject will be informed that they could be withdrawn from the study if they lose their medication

packaging a 2nd time. Second replacement packaging may be provided only at the discretion of sponsor and only under exceptional circumstances. No more than two replacements will be provided.

If for any reason subject's study drug supply ends up being insufficient to complete the study, subject should be scheduled for the last visit (24-month follow-up within 1 to 8 days of running out of study drug supply, preferably when subject has at least 1 remaining capsule of study drug ("1 day before running out". If this follow-up visit ends up outside of the visit window, it should be documented as a protocol deviation.

1.9.8.3 Lapse in treatment

If a lapse in treatment occurs, the days and duration that subject was off-treatment shall be documented. If the subject is off-treatment for a period longer than 4 weeks, and if subject lives relatively close to study site, study team may collect subject's plasma in an unscheduled visit to acquire pharmacokinetic data caused by lapse in treatment.

Lapse in treatment may occur for a variety of reasons, including health-related reason, temporary interruption, lost medication, subject forgetting to take treatment, study drug availability, family or personal reason, etc.

Lapse in treatment shall not result in modifications or postponing of subsequent follow-up visits, unless instructed by sponsor. Lapse in treatment may result in early withdrawal.

1.9.9 Study Drug Physical Description

Note: Drug may possibly be packaged in blister packs instead of HDPE bottles, in which case "bottle" or "packaging" in this protocol shall mean indifferently "bottle" or "blister pack." In addition, drug packaging may contain more than one month's worth of study drug, in which case study team shall adjust the quantity dispensed accordingly.

The study drug unit dosage is an opaque hard gelatin capsule. Color may vary by production lot. All capsules containing active ALK-001 or placebo look, weigh and smell the same and cannot be differentiated. Capsules are packaged and sealed in opaque plastic (HDPE) bottles with a child-resistant cap. Bottles may contain an oxygen scavenger pouch (or canister) and a cotton ball. Both cotton ball (and any residual cotton threads) and oxygen scavenger should be taken out of the bottle after breaking the seal and must be discarded. The oxygen scavenger is not needed once the seal has been broken.

Real-time stability data will be acquired throughout the study to ensure stability of all dispensed medications. Based on existing stability data acquired on previous batches of study drug, capsules are expected to be stable for at least 24 months. Bottles deemed to contain capsules out of specification may be collected by sponsor and replaced by new bottles.

1.9.10 Packaging and Labeling

Bottles delivered to the sites are expected to be labelled and require no further labeling. A sample of the label is found in section 1.22.1 and includes the following statement: "**CAUTION – NEW DRUG : LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE**." A medication ID corresponding to the randomization code (eg: GA2648) is printed on the label, along with dosage instructions for the study subject.

1.9.11 Testing, Tampering Study Drug Prohibited

It is prohibited to tamper with study drug, including used medication bottles and contents collected from subjects. Any unused study drug is the sole property of the sponsor and shall not be broken down, analyzed, or tested in any way.

1.9.12 Study Drug Supply: Receipt, Storage, Dispensing and Disposal/Return

1.9.12.1 Receipt of Drug Supplies

Sponsor will be responsible for coordinating the shipment of study drug to sites or study subjects.

Throughout the study, study team shall document receipt, storage, dispensing, and collection/return/disposal of study drug. Damaged or unusable study drug in a given shipment shall be documented and immediately communicated to sponsor.

1.9.12.2 Study Drug Storage

General storage and temperature monitoring: All study drug should be stored at room temperature, unless instructed otherwise by sponsor. Temperature should be monitored and recorded at least once daily with an appropriate device.

The study drug should be stored in a pharmacy, research pharmacy or in the investigator's office, as long as the study drug is stored in a locked cabinet/safe separate from FDA-approved medications, and the temperature is appropriately monitored. Because the product is light sensitive, the storage environment should not expose the study drug packaging to constant light or to direct sunlight. Study drug can be stored next to other investigational drugs. Everyone with direct access to the study drug should be listed in the regulatory binder.

For storing study drug collected from subjects, see section 1.9.12.4.

1.9.12.3 Dispensing of Study Drug; Direct to Patient Shipment

Dispensing by designated personnel only: For study drugs stored at the study site, study drug shall be dispensed only by designated personnel.

Two signatures required: To ensure that the proper medication ID is dispensed, dispensing shall preferably be performed by one designated person plus a witness checking that the proper medication is being dispensed.

First dispensing: At the end of the screening visit, which determines the beginning of the run-in period, a subject who receives the study drug for the first time should be provided instructions on storage conditions (room temperature, do not store in a car or in a sunny area, how to open the bottle/packaging, and at what time to take the study drug (preferably the same time as other medications. Subject should break the seal, discard the cotton ball if present (and any possible residual cotton threads, and discard the oxygen scavenger if present. The first capsule should be taken in front of the person dispensing the medication, and subject observed for approximately thirty minutes prior to being discharged.

Direct to patient shipping by site, research pharmacy or sponsor representative: study drug may be shipped directly to the subject by the study team, research pharmacy or by a sponsor representative. Study drug shall be packaged in standard unmarked cardboard boxes. Unless unavailable or impractical, which should

be documented, shipping to patient must be overnight, with direct signature required and delivery preferably in the morning. All study drug shipment shall be adequately logged.

Exposure of study team to study drug*:* ALK-001 is a vitamin A. Vitamin A is mildly teratogenic and is not considered a hazardous drug. No special precautions beyond reasonable care are required for the handling of the study drug. The study drug is formulated in an oil, self-contained in individual and sealed unit-dose capsules, packaged in a sealed plastic bottle, the content of which will only be accessed by the study subject. As such there is very little risk of environmental exposure of the study team to the study drug.

1.9.12.4 Collection from Subjects/Return of Study Drug

Collection of study drug from subjects: Subjects should be instructed to return all used or empty, partially used, or unused bottles to the study site at each visit. The number of remaining capsules should be recorded at time of return. Remaining capsules may be transferred into a freshly dispensed bottle of study drug unless directed otherwise by sponsor.

Storage of collected study drug: Study team will store all collected study drug until the end of the study or otherwise decided by sponsor. Study drug collected from subjects should be stored separate from the unused study drug (except when permitted by sponsor, and if such study drug packaging still contains unused drug, in a locked cabinet/safe/drawer accessible by designated personnel only.

If a subject has to permanently interrupt taking the study drug, all study drug shall be collected from subjects. Such collected medications should be stored at the site and not be administered to any other subject, unless directed otherwise by sponsor.

Return of study drug. The sponsor or monitor will pick-up these bottles, or they will be shipped to sponsor or to a designated facility for destruction, or destruction at the site will be requested, if feasible. No destruction should take place without request from sponsor.

At the end of the study, site close-out, or upon request by sponsor, unused study drug may be returned to sponsor or shipped to a designated address (including other study sites. Study drug packaging will be shipped using standard couriers such as UPS, USPS or Fedex. If necessary, sponsor will provide a temperature logger and specialized shipping containers and instructions.

1.9.13**Drug Accountability**

1.9.13.1 Drug supply

The study team will maintain records of study drug delivery to the site, study drug inventory, the number of bottles of study drug provided to each subject, the amount of unused study drug returned to the site by the subject, and the amount of unused study drug returned to the sponsor (or where otherwise mandated, a certificate of destruction of any unused study drug). Study monitors will verify the site's study drug and accountability records.

1.9.13.2 Study drug reconciliation

Subjects shall be instructed by study team to bring back all study drug to each follow-up visit. The study team shall then count all remaining capsules in subjects' bottles, and calculate the theoretical numbers of remaining capsules. Data will be recorded in the source document and any significant discrepancy investigated. If subjects forget to bring back all study drugs, study drug reconciliation cannot be performed and subjects shall be reminded to bring back all study drug to the next visit.

Discrepancy in study drug reconciliation or non-compliance with instructions shall be investigated by investigator and may result in withdrawal of a subject.

1.10 MONITORING OF COMPLIANCE

Compliance will be assessed and encouraged using the following means:

- *At each visit:*
  - Study team should discuss the importance of treatment compliance with subjects (daily drug intake, timing of drug intake, avoidance of vitamin A containing supplements, avoidance of vitamin A-rich items, and avoidance of other types of supplements except when permitted).
  - Study team should perform study drug reconciliation by counting the number of capsules remaining in the dispensed bottles and comparing this number to the theoretical number of capsules remaining.
  - Study team should remind subjects that they may be withdrawn from the trial at any time if they are thought to be insufficiently compliant.
- *Between visits:*
  - Study team will call subjects periodically to check compliance with the study drug and remind them of study instructions. This phone call should be made according to the Schedule of Events to the extent possible. Documented notes detailing the content of each phone call should be taken.

1.11 PRIOR AND CONCOMITANT MEDICATIONS; RESTRICTED FOODS AND MEDICATIONS

1.11.1 Prior (pre-treatment) and Concomitant Therapy

1.11.1.1 Prior medication or therapy (before randomization/treatment)

The investigator should record as prior medication or therapy all medications, including prescription and over-the-counter medications, vaccines, vitamins and supplements, taken by the subject from 30 days prior to the start of screening, up to the day of randomization. Investigator should also record any retinoid therapies taken up to 30 days prior to screening. This includes any vitamin A-containing supplements, accutane, acitretin, retinoic acid, bexarotene, and etretinate.

Preexisting clinically-effective therapies for a subject's existing condition must not be changed for the purpose of satisfying eligibility requirements and entering the subject into the study.

1.11.1.2 Concomitant medications and/or therapy (during treatment)

Starting from the administration of the first dose of the study drug, investigator shall record all concomitant therapies. These include prescriptions or over-the-counter medications, vaccines, vitamins, and supplements.

Efforts should be made to keep subjects' concomitant therapies stable throughout the study. Any change and reason for change in concomitant therapies should be documented.

1.11.2 Restricted Foods and Supplements

1.11.2.1 Vitamin A from liver and Vitamin A Supplements

1.11.2.1.1 Prohibited

Subjects will be informed **not** to consume:

- Food items that contain excessively large amounts of vitamin A. These include: **liver-based products** (including liver oil, liver sausage, foie gras, etc.), giblets
- **Vitamin A or beta-carotene containing supplements**.

At screening, the investigator should check whether the prospective subject has used vitamin A or beta-carotene containing supplements over the past 30 days. If so, prospective subjects must agree to stop in order to enroll into the study, and not take any vitamin A and beta-carotene containing supplements, at any dose, at any time during the study.

1.11.2.1.2 Allowed

Fruits and vegetables are allowed without any restrictions. They only contain carotenoids which are poorly absorbed and converted to vitamin A when taking preformed vitamin A.

1.11.2.2 Recommended: AREDS-2 or Equivalent. Prohibited: AREDS

At screening, the investigator should investigate the subject's use of AREDS (also known as AREDS-1) and AREDS-2 supplements.

AREDS is prohibited: AREDS contains beta-carotene, which is prohibited during the study. Subjects who are taking AREDS at screening should immediately stop taking AREDS until the end of the study.

AREDS-2 is recommended: AREDS-2 may slow the progression of intermediate to advanced AMD. In this study, AREDS-2 (or other brands that contain similar ingredients) is recommended for all patients, especially those with intermediate AMD in the fellow eye. Subjects who decide that they want to start taking AREDS-2 will be instructed to start taking it immediately. This is to avoid adding new concomitant medications during the study.

1.11.2.3 Discouraged: Other "eye" supplements

At screening, study team should investigate subject's use of supplements, and record supplements on the concomitant medication log. While not prohibited, supplements containing ingredients such as saffron, curcumin (turmeric), bilberry, resveratrol, CBD oil, and "multivitamins for vision" (except AREDS-2 and equivalent), are discouraged.

1.11.2.4 Discouraged: Over two (2) alcoholic beverages a day

Because alcohol consumption can result in accelerated metabolism and secretion of vitamin A by the liver, increasing the risk of adverse reactions [97], subjects will be encouraged to limit their alcohol consumption to two (2) alcoholic beverages per day.

1.11.3 Concomitant Medications, Prohibited and Restricted Medications, Participation in Other Clinical Trials

Prohibited (oral) retinoid therapies: Throughout the study, subjects are prohibited from taking any retinoid-based medications (including accutane, isotretinoin, acitretin, retinoic acid, bexarotene, and etretinate) except in the case of a medical necessity. Retinoids may trigger significant ocular and systemic adverse reactions, and could interfere with the pharmacokinetics or the mechanism of action of ALK-001.

Restricted medications: antibiotics of the class of tetracycline are known to interact with vitamin A. As such, tetracyclines should not be used by the subject unless no other class of antibiotics would be deemed efficacious. Tetracyclines include for example Demeclocycline (Declomycin), Minocycline (Minocin), Tetracycline (Achromycin), Doxycycline.

Prescription eyedrops allowed according to label and if medically necessary: Unless medically necessary, subjects are prohibited from using eyedrops except for over-the-counter lubricating eyedrops, for which there are no restrictions. When medically-necessary, FDA-approved prescription eyedrops may be used according to the approved label (no off-label use). Exception may be granted by sponsor, and should be documented.

Prohibited participation in other trials or studies: subjects are prohibited from enrolling or participating in any other clinical trials that involve a drug or treatment (investigational or not) for the treatment of GA, AMD or for any other condition, unless clinically necessary and recommended by the PI and approved by sponsor. Subjects are also prohibited from enrolling in studies that involve retinal imaging (see section 1.12.35.1).

Medication/Food/Drinks	During Treatment
Liver, liver oil, sausage, foie gras, giblets	Prohibited
Fruits & Vegetables	No restriction
Vitamin A or Carotene containing supplements	Prohibited
AREDS and AREDS-2 supplements	AREDS: prohibited AREDS-2: encouraged
Following supplements: saffron, curcumin (turmeric), bilberry, "multivitamins for vision" (Except AREDS-2), resveratrol, CBD oil	Discouraged
Following oral medications: accutane, isotretinoin, acitretin, retinoic acid, bexarotene, etretinate	Prohibited
Prescription eyedrops, except when medically necessary and according to FDA approved use	Only when medically necessary and according to drug label
Tetracycline antibiotics	Only if no other antibiotics class is available
Alcohol beverages	2 drinks max. per day

1.12 ASSESSMENTS AND ORDER OF PROCEDURES

Timing and schedule of all events is found in section 1.2. Details for each procedure are provided in this section, with practical details in the various manuals of operation.

1.12.1 **Primary Study Eye**

The PI and sponsor should agree on the choice of primary study eye by evaluating all inclusion criteria for each eye. The choice of primary study eye may later be changed based on the totality of data collected during the study (quality of imaging, conversion to CNV, reading center choice, etc.) but one eye must be selected prior to running efficacy analyses on atrophic lesions. The following guidelines, which may be amended from time to time in the manual of operations or the source documents, should be used to choose the study eye:

- *For subjects with only one eye that meets all "study eye" inclusion criteria*, that eye should be selected as the primary study eye.
- *For subjects with both eyes that meet all inclusion criteria*, the study eye shall be selected but the choice may be modified at the end of the study based on the following:
    - Well-delineated and accurately measurable atrophic lesions
    - Atrophic lesions likely to stay within the field of view over the next 2 years
    - Atrophic lesion border is closest to foveal center (in the case of foveal sparing)
    - Visual acuity is closest to the range 20/40 to 20/100.
    - Imaging availability and quality at all time points during the study

During the study, both eyes should undergo all procedures, or as described in the manual of operations.

1.12.2 **Order of Procedures**

Order of procedures will be provided in the manual of operations, which may be amended from time to time. General guidelines are provided here:

1. **Blood draw** should preferably be performed early if subject is fasting, but may be performed just before fluorescein angiography to avoid doing venipuncture twice that day.
2. **Patient-reported questionnaires** should preferably be conducted first upon subject's arrival, before subject has been dilated or has performed other vision tests.
3. **Undilated ocular tests** should preferably be performed in the following order:
    - **BCVA** (preferably using electronic visual acuity (EVA) system, although ETDRS charts are allowed upon approval by sponsor)
    - **Reading speed**
    - **Low luminance visual acuity**
    - **IOP** (may be performed just before dilation)
4. **Dilated ocular tests** should preferably be performed in the following order:
    - **Microperimetry**, (where available) should be performed as the first dilated test as the test requires subject cooperation. However, at screening, OCT has to be performed before microperimetry to locate the anatomical fovea that is required for placement of the microperimetry testing grid. Because microperimetry is sensitive to light or dark adaptation status, microperimetry must never be performed following fundus autofluorescence, dark adaptation, electroretinograms or color photo. However, if there is no other choice due to site logistics, at least one hour should lapse after performing fundus autofluorescence, or electroretinography before performing microperimetry. If a color photo is acquired by the microperimeter, there is no need to acquire a color photo with another camera.
    - **Keratometry**, (where available) should be performed once during the study to acquire ocular parameters
    - **SD-OCT**
    - **Fundus autofluorescence (FAF)**
    - **Fluorescein angiography (according to site or PI standard of care, to obtain all necessary imaging for the diagnosis of CNV)**

- **Color Photo**
- **Dilated ocular exam or assessment:** biomicroscopy, fundus exam, according to PI standard of care.
- **Treatment of CNV:** per PI standard of care.

Screening visit (V01) should preferably start early in the morning to allow sufficient time to complete all screening activities in a day. However, to reduce subject fatigue, for scheduling or planning purposes, or for any other reason, study team is permitted to complete the screening assessments over a period of multiple days, which is allowed as long as all screening activities are completed within 4 weeks from the first day of screening. In this case, all screening activities may be recorded on the screening "V01" source document template, but shall clearly indicate the date of actual performance of the procedure/assessment.

The following sections provide details about each procedure/assessment in the order they appear in the table of section 1.2.

1.12.3 Informed Consent

Before any study-related assessment is performed, study team shall go through an informed consent process with each prospective subject. At the end of the informed consent process, a subject must sign and date an IRB-approved informed consent form (ICF). See 1.19.3 for more details.

1.12.4 Demographics and Subject Characteristics

General demographic information shall be collected, including for example: date of birth, age, gender, ethnicity, race, highest education, household income, current or previous occupation if retired, smoking status, driving status, age of onset of GA, and age of onset of AMD.

1.12.5 Ocular Characteristics

The following ocular characteristics may be acquired during the study:

- **Refraction using an auto-refractometer (only at screening)**: for the screening visit, this is the preferred method to obtain starting refraction for BCVA. For follow-up visits, start from refraction obtained during screening BCVA.
- **Keratometry using an auto-keratometer (only at screening or only once during the study)**: measurement of corneal curvature should be done at sites where a keratometer is available. This may be done only once during the study, preferably at screening.

1.12.6 Fundus Features

At screening, PI shall review retinal images and evaluate the following features:

- Drusen
- Intermediate AMD
- CNV
- Reticular pseudodrusen
- GA lesions
    - Number of lesions
    - Foveal status
    - Total GA lesion area (approximate)
    - Hyperautofluorescent patterns in the junctional zone of GA

1.12.7 Medical, Surgical and Ocular History

1.12.7.1 General medical and surgical history

Systemic medical history will be elicited to establish an adequate baseline of pre-existing medical history, conditions, and symptoms. Medical history shall include preferably a complete review of systems, medical and surgical histories, and allergies using the below guidelines. Medical history will then be used to assess overall health, possible disqualifying medical conditions, and ability to participate.

For guideline, check in particular for the following medical history:

- History of poor intestinal absorption that could result from celiac disease, Crohn's disease, small-bowel resection, pancreatic insufficiency, intestinal bacterial infection
- History of prior gastrointestinal surgery except appendectomy, hernia repair or cholecystectomy
- Poor mental development or impaired cerebral function
- History of alcohol dependence or abuse
- History of liver disease, cirrhosis or poor liver function as measured on laboratory assays
- History of neurologic or neuromuscular disease
- History of hypotension or cardiovascular disease
- History of diabetes, chronic hyperlipidemia, hepatitis, pancreatitis
- History of ocular disorder that may confound assessment of the retina, such as cataract surgery within the past 6 months, CNV, glaucoma, recurring uveitis, diabetic retinopathy, diabetic macular edema, RPE tear, retinal vein occlusion, other retinal diseases, etc.
- History of chronic or ongoing conditions from the following categories:
    - Surgery (over the past 2 years)
    - Trauma (over the past 2 years)
    - Clinically-significant laboratory values from last 1 year, if available
    - Cancer/neoplasm
    - Allergies
- History of any condition that might interfere with the study treatment, prevent execution of the study procedures, or impair the ability of the subject to participate in the study for 24 months.

1.12.7.2 Ocular history and collection of historical retinal images and records

Thorough ocular history shall be collected from subjects, and historical results, records, data and photographs included in subjects' binders, to evaluate eligibility or for potential use in retrospective analyses. Ocular medical history shall contain:

- use of eye-related medication, including off-label and supplements
- previous or current participation in any clinical trial
- relevant ocular disorder or surgery (see general medical history above)
- age of onset of geographic atrophy
- age of onset of AMD
- quality of life/visual function questionnaires (preferably self-administered)
- results of historical tests since the time a subject started having geographic atrophy should be sought and requested from subject. If necessary, subjects may provide permission for their previous doctors to disclose these results to the study team. Data most important to gather are the following:
    - genetic test report(s) related to the eye
    - fundus autofluorescence imaging
    - microperimetry testing results

- color fundus photos
- OCT photos

1.12.8 Eligibility (Inclusion/Exclusion) Criteria

All enrollment criteria shall be reviewed between Screening (V01) and Randomization (V02) before randomization can be performed. If necessary, screening assessments may be completed on multiple days, up to the day of randomization.

1.12.9 Prior and Concomitant Medications

See section 1.11.

1.12.10 Adverse Events and Serious Adverse Events

At each visit or during check-up phone calls (section 1.12.11), study team should investigate new or ongoing adverse events (AEs) and Serious Adverse Events (SAE), and record such AEs or SAEs in an AE log. See section 1.16.1 for details on AE and SAE recording and reporting.

1.12.11 Monthly Phone Follow-up; Incoming Phone Call or Communication

Check-up Phone Calls:

- *On the day after the first dose*: To the extent feasible and preferably one day following the administration of the first dose of the study drug to a subject (during the run-in period), study team should call subject to check their well-being and remind them to continue taking the study drug at approximately the same time every day, for example at the time they take other daily medications (see section 1.9).
- *Preferably once a month thereafter*, study team should call subject, to assess general health, check or health-related concerns and AEs, concomitant medications, and compliance with study treatment; Subjects should be reminded of the schedule of future visits and to contact the study team for any health-related concerns, ocular and non-ocular, even if they believe it is not related to the study drug. In case a health-related concern is reported, PI shall determine if an unscheduled visit or a referral to a different physician is warranted (please refer to section 1.12.12 for details on unscheduled visits). In addition, if PI decides that a short/optional study visit can be skipped, subject may be informed of this decision during such phone call.

Incoming Phone Call or Communication: Subjects will be encouraged to contact the study team to report changes in health or health-related concerns. When a subject contacts the study team to report a health-related concern, via phone or other methods of communication (email or text message, for example), content of the communication should be documented. The same procedure as described above for Check-up Phone Calls should be followed: PI shall determine if an unscheduled visit or a referral to a different physician is warranted (please refer to section 1.12.12 for details on unscheduled visits). When a subject contacts the study team for purposes other than to relay a health-related concern (e.g. scheduling, general questions, etc.), this communication is not required to be documented.

1.12.12 Unscheduled Safety Visits

In case of health-related concerns, PI shall determine if an unscheduled safety visit should occur or if a referral to a different physician is warranted. There is no data or scientific evidence suggesting that the study drug would increase the chance of developing CNV. However, because subjects have GA at baseline, and may also have CNV, they are at risk of incidental CNV during their 2-year participation in the study. Additionally, due to their age group, subjects may develop other conditions that require a repetitive treatment. Thus, four scenarios, outlined below, may apply when a subject reports a health-

related concern. Investigator shall also refer to section 1.16 to determine if the below scenarios need to be documented as AE.

1) **If a subject has CNV at baseline**, the study team should attempt to synchronize the study visits with the subject's standard of care treatment schedule for CNV to the extent possible. For example, this may be done by scheduling visit V02 on the same day as a CNV treatment visit. Any visits that take place during the study where only CNV treatment is performed (i.e. those that may fall between study visits) do not require the assistance of the study team and will be considered "standard of care" and not be considered "unscheduled visits".
2) **If a subject has bilateral GA at baseline and later requires an unscheduled visit for a health-related concern that is <u>not diagnosed as CNV</u> and does not require repetitive follow-ups**, each such non-CNV health-related concern may involve the study team and may be considered an unscheduled visit.
3) **If a subject has bilateral GA at baseline and later requires an unscheduled visit for a health-related concern that is <u>diagnosed as CNV or another ocular condition,</u>** the initial unscheduled visit where the condition is diagnosed may be deemed an unscheduled visit. Subject shall receive routine care to treat or manage the condition. If prolonged or repetitive treatment is required, PI shall determine appropriate treatment according to their standard of care. Later treatment visits for that condition (i.e. those that may fall between study visits) will be treated as standard of care, do not require the assistance of the study team and will not be considered "unscheduled visits". Standard of care treatment records for these visits shall be included in subject binder. The study visit schedule should remain on track to the extent possible, but may be adjusted upon approval by sponsor to accommodate treatment of the subject's condition.
4) **If a subject reports a health-related concern that is <u>non-ocular</u> and PI believes such concern would be best addressed by a doctor of a different specialty or by the subject's PCP,** the study team should direct the subject to the appropriate physician. For example, if subject reports a cardiovascular concern, PI may direct subject to a cardiologist. Subject should be directed to follow-up with the study team and to provide medical records, and, if the health-related concern is deemed an AE, the event should be promptly listed and tracked on the AE log.

1.12.13 Optional Visits

The visit schedule may be challenging especially for visually-impaired, elderly subjects who live far from study sites. To reduce travel burden, PI may allow to skip visits V03, V05, V07, and V09, and request that study team performs a phone follow-up (according to section 1.12.11) or an in-person visit to subject's residence by study team, a home nurse or equivalent, as delegated by PI.

The above visits may be skipped by PI if PI does not have any safety concerns for a given subject based on review of ongoing AEs, and if subject is believed to be compliant with all study requirements.

1.12.14 Study Drug Reconciliation

See section 1.9.13.2

1.12.15 Vital signs

Intraocular pressure (IOP) shall preferably be acquired at each visit or at a frequency used by the site's standard of care. **Weight** (shoes off preferably) measured or converted in pounds (lbs), **height** (shoes off preferably) measured or converted in inches (in), and **body temperature** (preferably oral, measured or converted in Fahrenheit °F) should be acquired. Preferably after subject has been able to rest seated for approximately 5 minutes, **respiratory rate** (RR in breaths per minute), **heart rate** (HR in beats per

minute) and **blood pressure** (BP in mmHg) should be measured. Blood pressure should be taken seated, with the back supported, and both feet flat on the floor. Preferably, the left arm should be used. The same arm should be used at each follow-up visit whenever possible.

1.12.16 **12-lead ECG**

Vitamin A is not known to affect the ECG. ECG is performed to exclude patients who may have clinically-significant abnormal ECG at baseline, and annually to assess any clinically-meaningful ECG abnormalities. Note that ECGs are frequently interpreted as "abnormal" by the machine internal algorithm even for healthy subjects.

ECG Recording: A standard 12-lead resting ECG should preferably be taken supine to the extent feasible. Prior to taking the ECG, the subject shall preferably rest lying down in a quiet setting without distraction (no cell phone, no television) for a few minutes as they are being prepared for the ECG. During ECG recording, subject should not talk or move arms or legs. All recorded ECG traces must be printed out. The same ECG equipment should be used throughout the study if possible. Unscheduled ECGs may be requested by the PI if clinically-indicated.

Duplicate ECG when necessary: *If the ECG is interpreted by the machine as abnormal, or if the QTc is greater than 460 ms for male or 480 ms for female*, the person acquiring the ECG should verify all electrode placements and proper attachments, let the subject rest for 5 minutes, and record and print a second ECG trace. Both ECG traces should be printed out then interpreted and reviewed by PI or designated personnel. Special care should be taken during electrode placement, including skin preparation (shave extra hair, gently rub the skin to remove the dead skin layer).

ECG Interpretation: The ECG interpreter, who may be the PI or a designated person, should interpret all ECG printout(s) by (**a**) indicating whether the results are normal or abnormal, (**b**) providing comments if abnormal, (**c**) indicating which QTc value to use (otherwise the average of the QTc values will be computed) if more than one ECG trace was done **(d)** signing or initialing printout(s). The ECG interpreter may provide such information to study team via email, in which case email may replace signature.

ECG Final Review: PI is responsible for final review of the ECG by determining whether any abnormalities are clinically significant. PI should complete the following section to document ECG review.

Exclusion based on ECG: To prevent the enrollment of subjects with pre-existing heart conditions detected on ECG, subjects with QTc at screening greater than approximately 460 ms for male and 480 ms for female should not be enrolled in the study unless an approved exception is provided by sponsor.

Treatment interruption based on ECG: Treatment may be interrupted or discontinued based on ECG results according to section 1.14.4.

1.12.17 **Physical exam or Assessment**

Physical exam shall be performed by PI or other medically-licensed personnel authorized to perform physical examinations in the country or state of the site. A physical assessment may be performed by registered nurses in case an optional visit is performed at the subject's home. If possible, all physical examinations for an individual subject should be performed by the same personnel at each visit. The physical exam can be comprehensive (C) or simplified (S) (see table of section 1.2 for exact schedule)

- *Comprehensive physical exam* includes most body systems: general appearance, skin, ENT, head neck & thyroid, heart, lungs, chest, abdomen, extremities, lymph nodes, musculoskeletal, and neurological. Examination of genitalia, anorectal and breast exam is optional.
- *Simplified physical exam* includes general appearance, skin, ENT, head neck & thyroid, heart, lungs, abdomen, musculoskeletal.

Abnormal findings observed during the run-in period (from V01 to V02) shall be documented as medical history. After randomization takes place at V02, findings shall be documented according to section 1.16.

1.12.18 Ocular exam/evaluation (both eyes)

Eye exam/evaluation should be performed by PI or medically-licensed personnel on both eyes, according to standard of care practices, and should include:

- pupillary exam, unless the patient is already dilated at the time of exam,
- slit lamp exam,
- dilated fundoscopic exam.

Abnormal findings observed during the run-in period (from V01 to V02) shall be documented as medical history. After randomization takes place at V02, findings shall be documented according to section 1.16.

1.12.19 Best-Corrected Visual Acuity (both eyes)

Best-Corrected Visual acuity of both eyes should be acquired according to the manual of operations. In this study the "EVA" (Electronic Visual Acuity) system is preferred using the "non-study" mode (unless otherwise specified), although standard ETDRS charts may be used.

After a system (EVA, ETDRS or other) has been chosen, the same system must be used for all subsequent visits, unless otherwise approved by sponsor.

To obtain best-refraction, study team should preferably start from the refraction values obtained with an auto-refractometer (other possible methods include starting from the subject's glasses, plano, or historical refraction). For follow-up measures of BCVA, refraction should preferably start from the screening best-refraction.

1.12.20 Low Luminance Visual Acuity (both eyes)

Low luminance visual acuity should be acquired according to the manual of operations, using the same refraction and trial lenses used for BCVA.

1.12.21 Reading Speed

Reading speed tests shall be performed according to the manual of operations, with the subject wearing the same refraction and trial lenses used for BCVA.

The MNREAD and the International Reading Speed Test (IReST) [98] (and/or equivalent) may be used during this study. For IReST, English texts will be used, except if the subject strongly prefers a different language or does not speak English. The same language should be used at each visit and sponsor will designate which text to use for which visit.

1.12.22 Vision Questionnaires

Subject may be asked to complete the following vision questionnaires according to the manual of operations:

- Visual Functioning Questionnaire-25 (VFQ-25) (section 1.22.2),

- Functional Reading Independence (FRI) index (sample in section 1.22.3) licensed from Genentech,
- Other AMD and vision questionnaires.

The choice of visual function tests may be amended from time to time by sponsor.

1.12.23 Color Fundus Photograph (CFP)

CFP shall be performed at V01 according to the manual of operation. CFP shall be performed as clinically indicated at other follow-up visits.

1.12.24 Fluorescein Angiogram (FA)

At V01 and V10, investigator shall perform a fluorescein angiogram according to the manual of operations. At other visits, FA shall be performed as clinically indicated.

1.12.25 Fundus Autofluorescence FAF (both eyes)

This outcome measure is the primary endpoint. High imaging quality is required. FAF images should be acquired according to the manual of operations. FAF images acquired during the screening period must be promptly shared with sponsor or reading center to verify subject eligibility.

After randomization and start of treatment, FAF is a routine service to **investigate the progression of geographic atrophy lesions during the study, which is the primary endpoint of this study,** and to monitor regions of hyperautofluorescence that are indicative of those regions rich in vitamin A dimers and at higher risk of degeneration.

1.12.26 Spectral Domain-OCT (both eyes)

SD-OCT images should be acquired according to the manual of operations.

Important: OCT scans taken during the screening visit shall be immediately set as "reference," even in the absence of follow-up and before transfer to sponsor or reading center, so that follow-up images can be compared to initial scans. For follow-up visits, make sure the "follow-up" tool is used, and that the proper reference scans taken at screening (or last visit) are selected.

Throughout the study, OCT imaging is important as a **routine service to monitor or diagnose CNV and to detect changes not visible on FAF imaging** (such as changes in retinal thickness, photoreceptor layers, presence of sub- or intra-retinal fluid, etc.)

As such, both OCT and FAF are independently needed to monitor the safety of study subjects and to determine progression of their geographic atrophy.

1.12.27 Diagnosis and Treatment of CNV

PI shall follow standard of care practices to diagnose and treat concurrent or incidental CNV. Preferred diagnosis techniques include FA, OCT or OCTA. There is no known risk that the study drug would aggravate or accelerate CNV in a subject. As such, treatment with the study drug can continue when subjects have or develop CNV.

1.12.28 Microperimetry (both eyes, where available)

Microperimetry shall be performed according to the manual of operations, where microperimetry is available. Follow-up testing should use the "follow-up" function to ensure that the same anatomical points are tested and can be compared to values collected on previous visits.

1.12.29 Clinical Laboratory

Blood samples for chemistry, hematology, lipids, pregnancy (if performed), complement (optional), genetic (optional), and drug PK (or related substances) shall be collected according to the schedule of assessment. During repeat or unscheduled visits, blood samples may also be collected to test the below analytes or because of technical issues with the samples.

Subjects do not need to be fasting at the time of blood collection: if not fasting, subjects may have had a light breakfast and have consumed water to avoid dehydration. Subjects' fasting duration and number of hours elapsed since last study drug intake should be recorded. Blood samples should be handled according to a lab manual, labeled, then forwarded to either the central laboratory or the institution's designated laboratory for testing.

The PI must review all clinical laboratory reports and document this review by dating and signing off on the report, marking any abnormal value as clinically significant (CS) or non-clinically significant (NCS). Clinically-significant abnormalities measured after start of treatment should be recorded as AE (see section 1.15.7.2 for details).

Sufficient blood should be drawn to perform the following tests:

- Lipids:
  - Total cholesterol,
  - HDL,
  - LDL,
  - Triglycerides.
- Biochemistry:
  - Sodium,
  - Potassium,
  - Chloride,
  - Bicarbonate,
  - BUN,
  - Creatinine (with computed eGFR CKD-EPI),
  - Calcium,
  - Total Protein,
  - Total Bilirubin,
  - Albumin,
  - Alkaline phosphatase (Alk Phos),
  - AST,
  - ALT.
- Hematology:
  - Hemoglobin (HGB),
  - Hematocrit (HCT),
  - Mean corpuscular volume (MCV),
  - Mean corpuscular hemoglobin (MCH),

- Platelets (PLT),
- Red blood cell (RBC) count,
- White blood cell (WBC) count,
- Neutrophils (absolute and percent),
- Lymphocytes (absolute and percent),
- Monocytes (absolute and percent),
- Eosinophils (absolute and percent),
- Basophils (absolute and percent).

- Glucose:
  - Random glucose (optional)

Additional laboratory tests may be performed upon request by sponsor, or as clinically indicated by PI, but only after approval by sponsor (see section 1.17.12).

1.12.30 Vitamin A and Pharmacokinetics (PK)

Collection and processing of blood/plasma sample. The number of hours since the last study drug intake should be inquired and recorded. About 10 mL of blood will be collected in a K2-EDTA (purple top) tube. The tube will be pre-labeled and immediately covered with foil and placed in an ice bath if not immediately processed. The sample should be spun down for 10 minutes at 3,000-3,400 rpm or for the duration and at the rotational rate necessary to separate plasma, and plasma should then be transferred into 2 provided amber glass vials (one used as back-up in case of loss/damage), covered with foil, and immediately frozen.

At least 1 mL of plasma is required for proper testing. Because one (1) mL of plasma is necessary for proper testing of the plasma samples, the study team should ensure that at least one vial contains 1 mL of plasma.

Store frozen. Plasma samples should be stored frozen at approximately or below -20°C and preferably below -70°C for storage longer than 3 months, a duration which may be modified from time to time by sponsor.

Ship upon request. Periodically, the sponsor or representative will request the study team to ship available plasma samples to the bioanalytical lab, where a validated assay will determine the concentrations of various metabolites of ALK-001 and their corresponding non-deuterated vitamin A metabolites.

Lab manual to provide detailed instructions about the supplies, collection, handling and shipment.

1.12.31 Complement and Genotype

Blood or saliva samples will be collected according to the manual of operations, to measure complement activity and/or the subject's genotype (optional). Please refer to section 1.7.2.10 for details. Samples may be stored long term and pooled for analysis.

1.12.32 Pregnancy Test at Screening, No Contraception Requirements

Female subjects of childbearing potential will not be allowed to enroll in this study. For confirmation of absence of pregnancy before the start of treatment, PI may request a pregnancy test during the screening period.

There are no specific contraception requirements for subjects enrolled in the study. Nonetheless, if a male subject's female partner becomes pregnant during the treatment period, the pregnancy must be reported

to the sponsor within 24 hours of the site's knowledge of the pregnancy. Information on the pregnancy will be sought by the investigator until the end of the pregnancy (i.e. normal delivery, still birth, miscarriage).

1.12.33 Compliance (dietary and drug)

See section 1.10 for details.

1.12.34 Drug dispensing

See section 1.9.12.3

1.12.35 Other Procedures

1.12.35.1 Procedures/assessments prohibited outside of protocol

Subjects will be informed that they must not undergo any other ocular tests, exams or procedures, performed by any other optometrist or ophthalmologist who is not an investigator in the study, until the end of the study.

Except in case of a technical issue (eg: insufficient collected blood) or insufficient quality (eg: retinal imaging performed without following the manual of operation), or in the case of medical emergency or necessity which should be documented, investigator must not perform, allow, or request performance, of any procedure, ocular or blood, imaging, electrophysiological, psychophysical or any other test procedure or assessment that is not scheduled on the events table of section 1.2, unless an approvable exception is provided by sponsor, so as to preserve the integrity or quality of the data.

1.13 DETAILS ON STUDY VISITS OF INTEREST AND PHONE FOLLOW-UPS

1.13.1 V01 - Screening Activities and Run-in Period (2 to 4 weeks prior to randomization)

Screening activities will take place between V01 and V02, which shall be completed between 2 and 4 weeks (up to 28 days) prior to randomization. Randomization will take place on V02. To avoid screen failures, investigators should use their best judgment and only screen subjects they believe will meet all eligibility criteria. Investigator is given this 4-week buffer to allow for (i) review of FAF imaging, (ii) determination of eligibility, (iii) review of clinical lab reports, (iv) determination of initial approximate compliance, among others.

Screening: After the ICF has been reviewed, and all questions have been answered, the subject will have the opportunity to decide if they want to participate in the study and sign the ICF. The subject's informed consent must be obtained prior to the performance of any study-related procedures (See section 1.19.3 for details).
After obtaining consent, each subject will be assigned a unique screening ID number. This number will be provided by sponsor upon request by investor, unless sponsor informs site that the ID is sequential. The sponsor will inform each site of the subject ID format.

Subjects are then interviewed to determine their preliminary eligibility for enrollment by assessment of inclusion and exclusion criteria. If a subject meets these criteria, all procedures listed in Section 1.2 are performed. Investigator is encouraged to send the screened subject's fundus autofluorescence image(s) to

the sponsor or designated reading center as soon as possible to confirm that the subject meets the inclusion criteria.

Subjects' medical history shall be documented according to 1.12.7. In addition, historical retinal photographs (including for example FAF, OCT, etc.) shall be collected from subject and included in the subject's binder to help document historical progression of GA. If possible, such files may be received from other sites where subject has previously been seen, after proper authorization has been obtained.

Following screening activities and after receipt and analysis of all clinical laboratory results (excluding PK), all inclusion criteria and all exclusion criteria will be verified, and the subject will be determined as eligible to continue the study or will be withdrawn (screen failure). However, if a subject fails one entry requirement, if some clinical lab values were not properly tested (eg: due to a technical problem), or were inconclusive (eg. if the subject was not fasting or dehydrated at screening), or if retinal photographs or other baseline procedures were of insufficient quality, the investigator may choose to repeat the failed procedure (including re-test of laboratory value) to assess final eligibility.

Determination of initial approximate compliance during run-in period: After completion of activities from the first day of screening and if a subject has not yet failed any eligibility criterion, investigator should offer the subject a supply of placebo-containing capsules to assess compliance during the run-in period. Subject should not be informed that the capsules are placebo. Subject should be invited to return for V02, between 2 and 4 weeks after V01. At V02 and preceding randomization, compliance should be assessed and be deemed appropriate if it is greater than approximately 80%. If this is the case, a subject may be randomized and continue the study. If not, PI may decide to further discuss compliance with subject or to withdraw subject from the study.

If there are more eligible subjects than available spots for randomization, the decision about which subject to randomize will be based on practical considerations (distance to clinical site, subject schedule, imaging quality, technical data acquisition, etc.). Non-randomized subjects will be withdrawn from the study as "screen failure."

If a subject is a screen failure but is expected to meet all eligibility criteria in the future, subject may be rescreened upon agreement with the sponsor. Rescreened subjects will re-start the screening phase entirely, which will include receiving a new screening ID number and undergoing the informed consent process again, unless approved otherwise by sponsor.

1.13.2 V02 - Randomization Visit (Day 1)

On the day of randomization ("Day 1" or Visit "V02"), eligible subjects selected to participate in the treatment portion of the study are invited to return to the site (unless the medication is directly shipped to them). Subjects receive a "Subject ID" which is used to replace the screening ID. Subject ID will be provided by sponsor or representative, which may be provided orally.

To randomize a subject, investigator is given a sheet containing the list of assignable medication ID (masked), and simply assigns the next available medication ID to the subject (this is possible because blocks and treatment assignment will already have been created at the time of production of the randomization list). The investigator should inform the sponsor in advance so that the site can be properly supplied with study drug. See section 1.9.4 for details. An online randomization portal (IWRS) may be used instead of the paper-based randomization code.

The first bottle(s) of study drug can then be dispensed to the subject. Unless sent by email, the study drug is to be dispensed by the investigator or the clinical site pharmacy according to section 1.9.12.3.

The day after the first dose, study team should preferably call subjects to check their well-being and remind them to continue taking the study drug at the same time every day, according to section 1.12.11.

1.13.3 **24-hr PK testing authorized upon request by the sponsor**

Because it is unrealistic to perform a long-term pharmacokinetic study in healthy volunteers, detailed pharmacokinetic data of subjects who have been receiving ALK-001 for several months may be more readily acquired by including subjects participating in this study. For that, the investigator, SMC or sponsor might request that some subjects stay at the clinical site for a 24-hour overnight stay. Shorter than 24-hour stays may be admissible and should be agreed upon by the sponsor and the investigator on a case by case basis. Subjects should be informed with reasonable advance notice and should have the choice to accept or refuse to participate, which shall not affect their participation in this study. In case they accept, **the subject will sign a separate informed consent, which shall be IRB-approved**.

For each subject, blood samples should be collected at regular intervals (suggested: 2 and 4 hours post dosing, then every 4 hours for a total of 24 hours post dosing) and processed as described in the bioanalytical manual. In the case of an overnight stay and to reduce the burden on the clinical site, the subject might stay in another designated clinical site (such as a phase 1 unit for example) to perform such pharmacokinetic study.

To avoid unmasking, at least 3 subjects will be asked to participate in this PK sub-study, one in the placebo group, and two in the ALK-001 group.

1.13.4 **End of treatment period: optional open-label extension period**

Following completion of the initial treatment period of 2 years, subject may be given the choice to enter into a two-year open-label extension study. In order to enroll in this study, the subject will sign a separate informed consent, which shall be IRB-approved. Subjects who elect not to participate in the optional open-label study will be considered to have completed the study.

This optional study will assess the long-term pharmacokinetics of various dose levels of ALK-001, in order to estimate the smallest daily dose level that can maintain approximately 80% of deuterated vitamin A in plasma. In addition, fundus autofluorescence imaging will continue to be acquired and efficacy analyses on the growth rate of geographic atrophy will be performed on all subjects. This study will follow most standard of care practices. **Further details will be provided in future protocol amendments.**

1.14 SUBJECT RECRUITMENT, COMPLETION, EARLY DISCONTINUATION, WITHDRAWAL

1.14.1 **Subject Recruitment**

Identification: The investigator should use all IRB-permissible means to enroll subjects. The following recruitment channels are suggested:

1. Walk-in visits from new patients
2. Patients referred by colleagues in other locations or practices,

3. Patients referred by the sponsor or representative,
4. Investigator or clinical site's existing patients.

Pre-screen assistance: Sponsor or representatives will be available to assist the investigator in identifying subjects who might meet the eligibility criteria. This assistance may include for example the review of de-identified retinal images or medical charts.

Pre-qualification: Once a prospective subject has been identified, the investigator will reach out to the patient and follow an IRB-approved script to measure the interest of the patient for the study. If a prospective subject expresses an interest in participation, the investigator will review the protocol requirements and eligibility criteria with the subject.

A pre-qualification health questionnaire, typically used for standard practice in the investigator's office may be used by the investigator to pre-qualify subjects who could possibly meet the eligibility criteria. At that time, the investigator should use his/her best judgment so as to initiate screening only for subjects he/she believes would not end up being a screen failure.

Screening: If the prospective subject remains interested and may be eligible, he/she will be invited for the screening visit. Informed consent will be obtained by the investigator.

1.14.2 **Subject Completion; Early Discontinuation**

Subjects must remain in the study for the 24-month duration of the treatment period to be considered to have "completed" the study.

Subjects who permanently interrupt treatment before completing the study, or who are withdrawn from the study, will be considered to be "discontinued." Subjects who temporarily interrupt treatment may be invited by the investigator to resume treatment, in which case a protocol deviation shall be noted.

1.14.3 **Follow-up After Early Treatment Interruption; Early Termination Visit**

Subjects who temporarily interrupt treatment do not have any special follow-up and may simply continue according to the planned schedule.

Subjects who permanently interrupt treatment will be requested to return the study drug to the site (which may be done by mail), and may be invited to return to the site for an Early Termination visit (ET) (see section 1.2) if a minimum of approximately 1 month has elapsed following the last in-person visit. The ET visit should take place as soon as possible, preferably within 1 month of the permanent treatment interruption. During the ET visit, the following assessments shall be performed in addition to all routine care assessments:

- Physical and ocular examination
- AE
- Concomitant Medications
- Vital signs
- Collection of study drug
- Clinical lab (biochemistry, hematology, lipid, pharmacokinetics, and other optional testing as requested by sponsor)
- ECG: perform if previous ECG is older than ~4 months
- BCVA, LLVA, reading speed: perform if previous testing is older than ~4 months
- Fundus autofluorescence and OCT: perform if previous testing is older than ~4 months

- Microperimetry: perform if previous microperimetry is older than ~4 months
- Fluorescein Angiogram: perform if previous FA is older than ~one year
- Vision questionnaires: perform if previous questionnaires are older than ~6 months

Study team may consult with sponsor to determine if certain activities are required. At the completion of the ET visit, subjects' participation should be discontinued and all study drug returned to the site. There should be no additional follow-up visits.

1.14.4 **Temporary or Permanent Interruption of Treatment**

Abrupt interruption of treatment is not expected to adversely affect subject health and therefore no special precaution is needed when interrupting treatment. Sponsor shall be informed of any treatment interruption.

- If investigator and sponsor both agree that it is not in the best interest of the subject to continue treatment, for reasons including but not limited to, **non-compliance or health risk**, the subject shall interrupt treatment. Interruption may be temporary if the health risk is expected to resolve in a reasonable time. Subject may be allowed to resume treatment upon mutual decision by investigator and sponsor. In this case, off-treatment duration shall be documented.
- If subject's **treatment assignment is unmasked**, subject shall interrupt treatment, unless decided otherwise by sponsor.
- If a subject's level of **either AST, ALT or Alk Phos is greater than 5 times the upper limit normal (>5x ULN)** for laboratory reference range, subject should interrupt treatment immediately and permanently.
- If a subject's level of **either AST, ALT or Alk Phos is greater than 3 times the upper limit normal (>3x ULN)** for laboratory reference range, subject should be re-tested within 2 weeks. Temporary interruption of treatment is not required until re-test. If subject is unable to be re-tested within 2 weeks, subject should temporarily interrupt treatment until re-test can be performed. If at re-test, the obtained values are lower than 3 times the ULN, the subject can continue or resume treatment. If at re-test the obtained values are still higher than 3 times the ULN, the subject shall interrupt treatment, at least until these levels are measured to be below 3 times the ULN. Once this is the case, subject shall be allowed to resume treatment only upon approval by sponsor.
- Subject shall immediately interrupt treatment if subject is **presumed to have liver injury** according to Hy's law, as indicated by either of the following (assuming no other reason can be found to explain the combination of increase in aminotransferase and bilirubin, including for example alcohol ingestion, congestive heart failure, hepatitis, other drugs, preexisting liver disease, etc.)
    - ALT or AST greater than 3 times the normal upper limit, **with** total bilirubin greater than 2 times normal upper limit **and absent** of other causes of hyperbilirubinemia, **and absent** cholestasis (defined as alkaline phosphatase less than 2 times normal upper limit)
    - ALT or AST greater than 3 times the normal upper limit **with** clinical jaundice
- If during the study, a subject reports **pregnancy**, subject shall immediately and permanently interrupt treatment.
- If a subject's **QTc average value on duplicate ECG is greater than 500 ms or has increased by over 60 ms since the screening visit**, the subject shall temporarily interrupt treatment. Subject may resume treatment only upon approval by PI and sponsor.

If a subject interrupts treatment due to an adverse event, pregnancy or other medical reasons as described above, the subject must be followed at regular intervals until the adverse event normalizes, returns to the subject's baseline condition, or is considered to be related to normal progression of the

patient's condition or unrelated to the study drug. The sponsor and investigator will agree to an acceptable follow-up schedule for these subjects.

1.14.5 Lost to Follow-Up

A subject will be considered lost to follow-up if the following occurs:

- Subject misses 3 consecutive study visits (phone check-up and/or in-person visit),
- Subject cannot be reached by telephone following 2 consecutive missed visits (3 documented attempts by telephone made within ~2 weeks after the second missed visit), and
- Subject does not respond to the registered letter sent after the 3 attempted telephone contacts.

1.14.6 Withdrawal of Subjects from the Study

1.14.6.1 Reasons for withdrawal

A subject should be withdrawn from the study and participation discontinued, if any of the following occurs:

- *Screen failure (before randomization)*:
  - Subject has clinically-significant abnormal lab results at screening, unless approved by sponsor and PI
  - Subject has QTc>460 ms for male or >480 ms for female at screening, unless approved by the sponsor and PI
  - The investigator or sponsor is in the opinion that subject would not be appropriate for the study, for reasons including but not limited to, non-compliance during the run-in period, pre-existing condition or health risk.
- *Drop-out*:
  - Subject withdraws consent
- *Treatment interruption:*
  - Upon permanent treatment interruption, subject should be withdrawn after completion of a final follow-up visit, which should occur preferably within 1 month of treatment interruption (see section 1.14.3).
- *Unmasking*:
  - A subject's study treatment assignment becomes unmasked to subject, study team or the masked sponsor staff (except in the case of unintentional masking, in which case the sponsor and investigator shall decide).
- *Lack of compliance*:
  - Subject is unable or has not complied with intake of the study drug, except when approved by sponsor or in case of medication shortage
  - Subject misses a follow-up visit window and is judged by investigator as unable to comply with the visit schedule, except when approved by sponsor
  - Subject becomes pregnant
  - Subject has undergone eye examination(s) or imaging, outside the scope of this study, which in the opinion of the investigator could affect the progression of the disease or the procedures or data collected in this study, except when approved by sponsor (see 1.12.35.1)
  - Subject has received concomitant treatment, which in the opinion of the investigator may affect the progression of the disease or the procedures or data collected in this study, except when approved by sponsor.
- *Medical reasons*:

- The investigator and sponsor both agree that it is not in the best interest of the subject to continue participation, for reasons including but not limited to, non-compliance or health risk.
- Subject develops a medical condition that requires concomitant therapy with a prohibited medication (See section 1.11.3).
- Subject develops a life-threatening adverse reaction, or a serious adverse reaction that places them at immediate risk.
- Subject permanently interrupts treatment according to one of the reasons of section 1.14.4.
- Subject experiences a QTc interval > 500 ms or an increase of QTc greater than 60 ms, based on average QTc value of duplicate ECG, except if approved by sponsor.
- Subject is dead.

- *Lost to follow-up:*
  - Subject is lost to follow-up, after every reasonable effort has been made by the study team to contact the subject and determine the reason for discontinuation/withdrawal. All efforts and measures must be documented.

1.14.6.2 How to withdraw a subject and discontinue study participation

If a subject is to be withdrawn from the study and participation discontinued:

- subject is asked to stop taking the study drug,
- an early termination visit should be scheduled within approximately 1 month following the administration of the last dose of study drug (see section 1.14.3), and
- all remaining study drug should be returned to the site, including all empty bottles, partially empty bottles, or unopened bottles,
- investigator should make reasonable efforts to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights.
- All findings should be fully documented.

All study drug returned by the subject should not be used or administered to another subject, except upon written request by the sponsor.

1.14.7 **No Replacement of Subjects**

Withdrawn subjects will not be replaced by new subjects, except upon written request by the sponsor. Therefore, it is important to only enroll participants who are likely to adhere to the schedule of the study visits, to the self-administered treatment regimen, and to the procedures performed during the study visits.

1.14.8 **Data Collection**

All data collected up to the day the subject was withdrawn will be used.

1.15 STATISTICAL METHODS

A statistical analysis plan (SAP) will be generated before data analysis and will describe all planned statistical analyses. The **SAP should supersede the below statistical sections of this protocol in case of discrepancies between such sections and the SAP.**

1.15.1 **Sample Size Determination and Power Calculation**

Sample size calculation was based on review of all available literature data on the progression of GA. With 300 subjects enrolled in the study and assuming that 80% of subjects are evaluable for the primary outcome measure, the study has an 80% power to detect, after 24 months of treatment, a 33% slowing in

GA growth rate with a 2-tailed significance of 0.05, assuming a conservative standard deviation of 1.5 sqmm/year and an average GA growth rate of 1.8 sqmm/year in the control group.

As part of the exploratory measure, and assuming that 35% of enrolled subjects have a fellow eye with active or history of CNV, the study has an 80% power to detect, after 24 months, a 75% reduction in incidental progression to CNV in the study eye with a 1-tailed significance of 0.2 (Fisher's exact test).

1.15.2 Interim Analysis

Interim efficacy analyses, if any, will be performed according to the SMC charter and the statistical analysis plan. Safety data will be reviewed periodically by the SMC as described in the section below.

1.15.3 Safety Monitoring Committee (SMC); Interim Data Analyses

An independent SMC will be established to monitor the study data on an ongoing basis and to ensure the continued well-being of subjects enrolled in this study. The committee shall meet periodically, but no less than once a year, to review safety data. SMC may organize ad hoc meetings if required, or may change the frequency of meetings based on findings, enrollment or other factors.

The SMC may make recommendations about the study design or execution. A SMC charter shall supersede this protocol in case of conflict. The SMC shall be composed of at least 3 members, with no less than 2 voting members. To ensure proper masking of the study team, investigators, study team, sponsor staff who interact with the investigators and/or subjects, cannot be members of the SMC. The SMC should consist of at least 1 medical expert in the field of ophthalmology and at least 1 statistics expert. SMC members may be amended from time to time.

SAEs will be communicated on an ongoing basis to the SMC. The SMC may have access to unmasked data upon request and review tabulated summaries and any additional data the SMC may request during the study. The sponsor, representative and monitors should review masked data from the sites and notify the SMC of any issues relevant to subjects' health. In no event should current or former SMC members communicate unmasked data, results, analyses or randomization code to anyone outside of the SMC.

Content of summaries, SMC role and responsibilities and general procedures, including communications and recommendations on the study conduct, will be defined and documented in the SMC charter. Initial charter and SMC members shall be organized within approximately 6 months from the enrollment of the first subject in this study.

1.15.4 Datasets

Analyses should be performed on the following datasets as appropriate and as described in the Statistical Analysis Plan:

- *Intent to treat (ITT)*: All randomized subjects who receive at least one dose of the study drug.
- *Per protocol (PP)*: All randomized subjects who have completed the study generally in accordance to protocol, as determined by sponsor. The decision of whether a subject is included in the PP group will be made after all data have been verified and before data analysis.

1.15.5 General Principles

Individual subject data will be presented in the data listings. The listings shall include all subjects who were randomized and may exclude all the other subjects.

Summary statistics will be used to describe:

- *Continuous data*: the number of observations (N), mean (mean), standard deviation (SD), median (median), minimum value (min), and maximum value (max). The precision of the measurement unit for each variable will be used to determine the number of decimal places used to report those summary statistics. Min and max will be reported with the same precision. Mean and median will be reported to 1 greater decimal place, and the SD to 2 greater decimal places. Values that require conversion will be converted with the appropriate precision.
- *Categorical data* will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Missing or incomplete data will be handled as described in the Statistical Analysis Plan.

1.15.6 Demographics and Baseline Characteristics

Treatment groups will be described and compared with respect to demographics and baseline characteristics (including for example: age, sex, race, weight, height, genotype, phenotype, GA lesion characteristics, microperimetry, smoking status, etc.). The Statistical Analysis Plan will provide details on all analyses.

1.15.7 Safety Analyses

Safety data will be assessed by summarizing the number and proportion of subjects with AEs and the types of AEs, using standard coding. The following are guidelines on how the information will be analyzed. Variations are acceptable, as long as the final report is representative of available data. The Statistical Analysis Plan will provide details on all analyses.

1.15.7.1 Adverse events

Verbatim terms of AEs recorded by study team will be coded by sponsor using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 (most recent version available at the time of the first version of this protocol) or more recent. AEs with onset (or worsening) during the treatment period, i.e. AEs experienced by subjects who have received at least one (1) dose of study drug after randomization will be included in the analysis. AEs recorded prior to the first administration of the study drug or during the run-in period will be considered part of "medical history."

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, interrupt treatment due to an AE, or who experience a SAE.

1.15.7.2 Clinical Laboratory Tests

Laboratory data will be summarized by analyte. Descriptive statistics will be calculated for selected laboratory analyte at screening and at each scheduled time point.

1.15.8 Pharmacokinetic Analyses

Collection of plasma samples: After venipuncture, blood sample shall preferably be kept on ice until it is spun down and plasma is extracted. Extraction of plasma should occur preferably within one hour of venipuncture. Plasma must be stored at below approximately -20C in amber glass vials and shipped periodically to the bioanalytical lab, as instructed by sponsor or representative. *Details are provided in the bioanalytical manual*.

Analyses: The following metabolites of vitamin A (non-deuterated) and ALK-001 (deuterated) will be measured by a bioanalytical lab throughout the study: retinol, retinyl palmitate, retinoic acid. Data will be summarized and presented in plasma absolute concentrations (ng/mL) as well as in % deuterated.

1.15.9 **Efficacy Analyses**

As the primary endpoint, the growth rate of geographic atrophy lesions between baseline and 24 months will be presented. The study is powered to detect a ~33% reduction in the growth rate of atrophy between placebo and ALK-001. The Statistical Analysis Plan (SAP) will provide details on analysis techniques and statistical code. The SAP will be submitted to regulatory authorities before analyses are performed.

1.16 ADVERSE EVENTS

1.16.1 **Definition of Adverse Events**

Definition. An adverse event (AE) or "Treatment Emergent Adverse Event" (TEAE) is defined as any untoward medical occurrence in a subject that occurs after randomization (V02) or due to the performance of a protocol-specific procedure or assessment, *whether or not it is caused by the study drug*. Medical occurrences that occur prior to V02 or are not due to protocol-specific procedure or assessment will be considered part of medical history.

Examples of AE:

- Observed by study team:
  - A clinically-significant abnormality in physical or ocular examinations
  - A clinically-significant finding in ECG, vital signs
- Reported by subject:
  - A subject-reported new symptom, injury, or disease
  - A preexisting condition that has worsened (increased in severity, frequency or pattern), unless judged by the investigator as consistent with the natural progression of the preexisting condition.
- Measured in clinical lab:
  - Deterioration in a laboratory value or other clinical test associated with symptoms or leads to a change in study treatment or concomitant medication (See section 1.16.1.6).

1.16.1.1 Collection and Documentation of Adverse Events

Collection of AE should occur according to the events table (Section 1.2). During all instances of communication with subject, including phone calls or other forms of communication, study staff shall inquire about health-related concerns through non-directive, non-leading questions. Examples of non-directive questions include the following:

"How have you felt since your last visit / since we last spoke?"
"Have you had any new concerns or changes in your health since you were last here / since we last spoke?"

Study team should then determine if such concerns are AEs and if so list AEs on the AE log, and PI should determine if an unscheduled safety visit or a referral to a different physician is warranted (See section 1.12.12). AE or health-related concerns may also be spontaneously reported by subjects between visits or during visits while undergoing physical or ocular examination, ECG, blood draw, or other assessments.

Follow-up monitoring of AEs: Study team should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws

consent. Every effort should be made to follow all AEs or SAEs considered to be possibly-related or related to study drug, until a final outcome can be determined. After a subject discontinues participation, study team should follow AEs according to 1.16.1.5.

Documentation of AE: Information on AEs should be documented in source documents, with sufficient details and notes to allow adequate understanding of the AE dates, status, clinical diagnosis, signs, symptoms, body part involved.

Recording and updates: Study team shall avoid colloquialisms and abbreviations in the AE description. Not all information regarding the AE may be available at the time the AE is detected or documented (including for example: definitive diagnosis, dates of AE, AE outcome, action taken, or causality to study treatment). Such information should be recorded as soon as it becomes available. See section 1.16 for details.

Description of the event: When recording AEs, study team should use correct medical terminology and concepts. AEs may fit into different categories based on available information:

Definitive diagnosis: If a clinical diagnosis is known and confirmed by investigator, record the diagnosis. Study team may also list signs and symptoms in a side "note." (eg: record "hepatitis" if known to be the diagnosis rather than "jaundice, asterixis, and elevated transaminases").

Definitive diagnosis along with signs/symptoms not normally associated with the diagnosis: If any signs or symptoms are not normally associated with the definitive diagnosis, study team shall list these signs/symptoms in separate AEs.

Presumed/Provisional diagnosis: If at the time of report, a diagnosis is unknown or unsure, study team shall record in a single AE, the provisional diagnosis as well as the reported signs/symptoms (eg: "presumed influenza with low grade fever"). If a clinical diagnosis becomes later known and confirmed by investigator, AE should be updated to indicate the definitive diagnosis.

Constellation of signs or symptoms that cannot be characterized as a single diagnosis: study team shall record each individual sign and/or symptom as its own event. These AEs should be updated if a diagnosis is later determined

AEs occurring secondary to a primary event: in general, in case of a cascade of events or clinical sequelae, study team shall record the primary cause, with the exception of severe or serious secondary events, or medically significant AEs occurring at separate points in time, which shall be recorded separately. For example:

- *If vomiting results in mild dehydration with no additional treatment, only vomiting should be recorded.*
- *If vomiting results in severe dehydration, both events should be recorded separately*
- *If dizziness leads to a fall and consequent fracture, all three events should be recorded separately*

Recording of AE Parameters: For each AE, study team should record:

- Verbatim description of the event (including either *definitive* diagnosis with signs/symptoms in notes, or a *provisional* diagnosis, along with signs and symptoms in the verbatim description, when a definitive diagnosis is not known)
- Start Date/Time
- Is the AE ongoing or not?
- End Date/Time
- Is the AE "serious" or "not serious" (see section 1.16.3)
- AE severity (see section 1.16.1.11)

- Frequency/Pattern (Single event, Intermittent, continuous)
- Action taken related with study treatment (see section 1.16.1.13)
- Action taken unrelated with study treatment (see section 1.16.1.15)
- AE outcome (see section 1.16.1.14)
- AE causality to study treatment (see section 1.16.1.12)

- Did AE cause subject to withdraw from the study?

1.16.1.2 Worsening of Geographic Atrophy and AE

Events consistent with expected pattern of progression of Geographic Atrophy or AMD should not be recorded as AEs.

Worsening of Geographic Atrophy. Medical occurrences or symptoms of deterioration anticipated as part of normal progression of GA should be recorded as AE only if judged by investigator to have unexpectedly worsened in severity or frequency or changed in nature during the study. When recording an unanticipated worsening of GA, study team should emphasize that condition has unexpectedly changed by including applicable descriptors (eg: "accelerated GA").

1.16.1.3 Presence, Development and Worsening of CNV in either eye

Subjects with Geographic Atrophy are at risk of developing CNV, with a higher risk if one eye has concurrent or a history of CNV. As such:

- Clinical changes in pre-existing CNV ***consistent*** with expected progression of CNV should not be recorded as AEs.
- Clinical changes in pre-existing CNV ***inconsistent*** with expected progression of CNV should be recorded as AEs.
- Development of CNV in an eye that has no history of CNV should be recorded as AE.

There is no expectation that the study drug would aggravate or accelerate CNV in a subject. As such, treatment with the study drug should continue in case of CNV-related AE.

1.16.1.4 *Preexisting Condition(s) and AE*

Preexisting condition known or discovered at screening or during the run-in period. A preexisting condition is one present prior to or identified during the screening or run-in period, before the first study drug is administered (V02). *Preexisting conditions should be recorded as "Medical History."*

Clinically-significant abnormality during the screening period. Any clinically-significant abnormality (eg: lab value, ECG, physical exam, etc.) identified during screening or run-in period should be recorded as part of the subject's medical history.

Preexisting condition discovered during the treatment period. Because patients may sometimes fail to report, or the investigator may fail to detect all preexisting conditions during the screening period, preexisting conditions discovered during the treatment period shall also be recorded as part of the subject's medical history.

Changes in a condition marked as preexisting condition (other than AMD/CNV or Geographic Atrophy). During the treatment period, a condition previously recorded as a preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens after the administration of the first dose of study drug, or if any new clinically-significant findings/abnormalities that meet the

definition of an AE are observed. Progression of the disease consistent with the disease natural history shall not be considered an AE.

1.16.1.5 Post-treatment AE - Appropriate Medical Care and Relevant Follow-up After the Trial

Following the end of treatment with the study drug, all unresolved SAEs, or any unresolved AEs judged by investigator to be "related to the study drug" should be followed by study team until the events are resolved, return to baseline, become stable or a chronic condition, or the subject is lost to follow-up.

At the last scheduled visit, investigator should instruct subjects to report any future event(s) that may possibly be related to the study treatment as determined by the subject or the subject's personal physician.

The investigator should notify the sponsor of any death or AE occurring at any time after a subject has discontinued or completed study participation, as long as such event may be possibly related to the study drug. The sponsor should be notified if the investigator becomes aware of the development of cancer.

1.16.1.6 *Abnormal Clinical Laboratory Values*

Not every laboratory abnormality qualifies as an AE. Non-drug related laboratory abnormalities occur spontaneously in clinical trials [99-101]. For example, the probability of a random elevation of AST, ALT, or AP to two times the upper limit of normal is 0.67% in one single subject; this probability of random elevation becomes 87% in a trial of 300 subjects [101]. Therefore, a clinical laboratory abnormality should be documented as an AE only if it meets any of the following:

- The abnormality is accompanied by clinical symptoms,
- The abnormality is judged clinically-significant by investigator,
- The abnormality suggests a disease, syndrome, and/or organ toxicity that is new or has worsened from screening, or
- The abnormality requires a therapeutic or medical intervention (e.g. change of dose, interruption of treatment, more frequent follow-up assessments, and further diagnostic investigation).

Investigator shall be responsible for reviewing all laboratory findings and exercise medical and scientific judgement to decide whether an isolated laboratory abnormality should be classified as an AE.

Recording in case an abnormal clinical lab value is judged an AE:

- If an abnormality is a sign of a disease or syndrome that is new or has worsened from screening, only the diagnosis should be recorded.
- If an abnormality is judged clinically-significant and is not a sign of a disease or syndrome, the abnormality itself should be recorded along with a descriptor indicating if the test result is above or below normal range (eg: "elevated potassium" as opposed to "abnormal potassium"). If a precise clinical term exists, the precise clinical term should be recorded as the AE (eg: elevated potassium level of 7.0 mEq/L should be recorded as "hyperkalemia.")
- Repeat observations of the same abnormality from visit to visit should be recorded only once, unless the etiology changes. The initial severity of the AE shall be recorded, and the severity and seriousness updated any time the event worsens.

1.16.1.7 Abnormal Vital Sign or ECG Values

Not every vital sign or ECG abnormality qualifies as an AE. An abnormal vital sign or ECG result shall be documented as an AE if it meets any of the following criteria:

- The abnormality is accompanied by clinical symptoms,

- The abnormality is judged clinically-significant by investigator,
- The abnormality suggests a disease, syndrome, and/or organ toxicity that is new or has worsened from screening, or
- The abnormality requires a therapeutic or medical intervention (e.g. change of dose, interruption of treatment, more frequent follow-up assessments, and further diagnostic investigation).

If a clinically-significant abnormality (e.g., high blood pressure) is a sign of a disease or syndrome, only the clinical diagnosis (i.e., hypertension) should be recorded. Otherwise, record the abnormality itself.

Investigator shall be responsible for reviewing all vital sign and ECG findings and exercise medical and scientific judgement to decide whether an isolated abnormality should be classified as an AE. If classified as an AE, it shall be recorded according to section 1.16.1.1.

1.16.1.8 Deaths

Deaths that occur during the AE reporting period must be reported in a SAE report. Death should be considered an outcome of an AE, and not a distinct AE. The event or condition that caused or contributed to the fatal outcome, if known, should be recorded as the single medical concept. Generally, only one such event should be reported.

- The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable.
- If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded.
- If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

1.16.1.9 *Pregnancy*

Pregnancy is not considered an AE.

Subjects enrolled in the study are 60 years old and over and should not be of childbearing potential. However, in the unlikely case a subject becomes pregnant during the study, subject must immediately and permanently interrupt the study drug. All reports of pregnancy of female subjects or male subject's female partner must be reported to the sponsor within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (eg: spontaneous abortion, stillbirth, congenital anomaly) are considered SAEs and must be reported.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

1.16.1.10 *Hospitalization, Prolonged Hospitalization or Surgery*

Unplanned hospital admissions resulting from an AE shall be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition leading to surgery should be documented as an AE if the condition meets the criteria for an AE.

In the case of diagnostic or planned/elective surgical procedures for a preexisting condition, neither the preexisting condition, hospitalization, prolonged hospitalization, or surgery shall be recorded as an AE.

1.16.1.11 Adverse Event Severity

Investigator shall determine and record the severity of all AEs and SAEs.

Only after an event has been deemed to be classified as AE (see above section), study team may use the most up to date version of the Common Terminology Criteria for Adverse Events (CTCAE) for grading the severity of adverse events. Adverse events of CTCAE Grades 4 and 5 should be documented as "life-threatening." A copy of the CTCAE will be provided.

AEs that do not appear in the CTCAE should be determined according to the following definition:

- Mild (Grade 1): Awareness of the event; may cause minimal interference with the subject's daily life; requires minimal or no treatment.
- Moderate (Grade 2): Discomfort enough to cause a noticeable impact on the subject's daily life; results in a low level of inconvenience or concerns with the therapeutic interventions.
- Severe (Grade 3): Incapacitation or significant impact on the subject's daily life; may require systemic drug treatment or other treatment.
- Life-Threatening (Grade 4): Subject in immediate risk of death from the event as it occurs.

Note: Regardless of severity, some events may also meet seriousness (SAE) criteria. Refer to definition of a serious adverse event (see Section 1.16.3).

1.16.1.12 Adverse Event Causality / Relationship With Study Drug

PI shall use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes, to determine the relationship between the study treatment and the AE using the following criteria:

- Unrelated: This relationship suggests no association between the study treatment and the reported event. Another factor is clearly involved.
- Unlikely related: This relationship suggests a disease, other drugs or other factors may have produced the event; event may or may not follow a plausible temporal sequence with the study treatment; there is insufficient or contradictory information about the event which prohibits a proper assessment.
- Possibly related: This relationship suggests that the study treatment contributed to the AE; the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study treatment, but could also have been produced by a disease, other drugs or other factors; information on drug withdrawal may be lacking or unclear.
- Probably related: This relationship suggests that the study drug has caused the AE. A reasonable temporal sequence of the event and the study drug administration exists. This assessment will be based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the investigator's clinical experience.
- Definitely related: This relationship suggests that a definite causal relationship exists between the study drug administration and the AE. Other conditions (concurrent illness, progression of disease state, or concurrent medication reaction) do not appear to explain the event.

In their assessment of study-drug causality, investigator shall take the following guidance into consideration:

- Temporal relationship of event onset to the initiation of study drug

- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug
- Known association of the event with study drug or similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject, or use of concomitant medications known to increase occurrence of the event
- Presence of non-treatment-related factors known to be associated with the occurrence of the event.

1.16.1.13 *Study Treatment Action Taken*

Investigator shall classify action(s) taken related to study treatment with regard to the AE. Action(s) taken should be classified according to the following categories:

• None: Study drug dose not changed in response to the adverse event.
• Temporarily Interrupted: Study drug administration temporarily stopped in response to an AE. If study drug administration is not-restarted, "action taken" changes to "Permanently Interrupted."
• Permanently Interrupted: Study drug administration permanently stopped in response to an adverse event.
• Not Applicable: Action taken regarding study drug administration does not apply (for example in circumstances such as when the subject has died, or the treatment has already been completed before the adverse event).
• Unknown: Action taken is unknown (for example for a subject treated at a hospital not under the care of the investigator and investigator has no knowledge whether study drug was continued or not).
• Dose reduction: Dose of study drug is reduced, without interruption of treatment.

1.16.1.14 *Adverse Event Outcome*

Investigator shall document the outcome of AEs using the following categories:

• Recovered: Resolution of an AE with no residual signs or symptoms.
• Recovered with Sequel: Resolution of an AE with residual signs or symptoms.
• Recovering: The AE is ongoing and continuously improving but is not fully resolved.
• Not Recovered: The AE is ongoing and does not show any sign of improvement or no improvement.
• Fatal: Outcome of an AE is death (when death is at least possibly related to the adverse event).
• Unknown: Outcome of an AE is unknown (for example when a subject is treated at a hospital not under the care of the investigator and the investigator has no knowledge of the outcome of the adverse event).

1.16.1.15 *Treatment Given*

Investigator shall describe whether any treatment was given for the AE unrelated to study treatment. Treatment may include other medications, hospitalization, surgery or physical therapy. If medication was used, the generic name, dose, duration, and frequency should be recorded in the concomitant medication log.

1.16.2 Medical Monitoring by PI

PI shall oversee the well-being of subjects enrolled at their site and be responsible for ensuring that all AEs are recorded and monitored in accordance to GCP and this protocol. However, study team and sponsor are encouraged to discuss patient safety cases.

1.16.3 Serious Adverse Events

A serious adverse event (SAE) is any AE whose outcome meets any of the following criteria:

- **Fatal** (death, regardless of cause, which occurs during participation in the study, or occurs after participation in the study and is suspected of resulting from a delayed toxicity due to administration of the study drug);
- **Life-threatening** (subject was at immediate risk of death; laboratory abnormality of Grade 4 are not SAEs unless the clinical status of the subject indicates a life-threatening AE);
- **Requires inpatient hospitalization or prolongation of hospitalization (**with the exception of planned/elective hospitalization);
- Results in:
    - **Persistent or significant disability or incapacity** (disability defined as substantial disruption of a subject's ability to conduct normal life functions);
    - **Congenital anomaly or birth defect;**
    - **An important medical event** clearly of major clinical significance although it may not be immediately life-threatening. An important medical event may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered important medical events.

"Severe" adverse events are not synonymous of SAE: Severe indicates the severity grade (see section 1.16.1.11), such as in a *mild*, *moderate* or *severe* headache. Headaches are of minor medical significance and would not be considered to be serious adverse events. Serious adverse events are defined by the *outcome* of the event, outcome that poses a threat to a subject's life or functioning.

1.16.3.1 Reporting of Serious Adverse Events by Investigators

Study team shall record SAEs on SAE report form provided by sponsor. Information will include at minimum the following: subject date of birth, age at the time of the onset of the SAE, sex, weight, outcome(s) attributed to the SAE, onset and stoppage date, location the SAE took place, whether the SAE was unexpected, a narrative description of the event (including relevant signs/symptoms, progression, treatment, outcome), relevant tests/diagnoses, other relevant medical history, medications used at the time of the SAE, relatedness to study treatment, action taken related to study treatment, rationale as to why the event is considered serious. Copies of relevant records should be added to the form, with all confidential or identifiable information removed. The subject ID and initials should be written on such records. Follow-up information on the SAE may be requested by sponsor.

The SAE report form must be sent to sponsor within 24 hours from the point in time when the investigator becomes aware of the SAE. If not all information is available at the time the SAE report is created, follow-up information should be submitted within 24 hours of their receipt.
Report SAEs by phone and fax to:

[redacted]

This contact information may be amended from time to time, and the latest information will be found in the regulatory binder.

1.16.3.2 Investigator reporting: notifying the site or central IRB

Investigator shall abide by IRB notification rules concerning the reporting of AEs and SAEs.

1.16.3.3 Sponsor reporting: Notifying the FDA

Following receipt of SAE report and whenever required by 21 CFR 312.32, sponsor will report the SAE to FDA on form 3500A and send a copy of the form to the investigator. Study team shall keep a copy of this form 3500A on file.

Whenever required by law, the sponsor will report certain study AE to the FDA in IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening, and

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting:
If available, the sponsor will identify in the IND safety report all previous reports concerning similar AEs and will analyze the significance of the current event in light of such previous reports.

1.16.3.4 Sponsor reporting: Notifying participating investigators

Sponsor shall notify investigators, in a written safety report, of any serious adverse event that is both unexpected and for which there is a reasonable possibility that the drug caused the event, as well as any findings from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsor shall analyze the significance of such event in light of previous reports, if available. “Reasonable possibility” shall be interpreted according to 21 CFR 312.32(a) as “evidence to suggest causal relationship between the drug and adverse event.”

1.17 ADMINISTRATIVE REQUIREMENTS, DATA HANDLING AND RECORD KEEPING

1.17.1 Trial-Specific Materials

Without limitations, trial-specific materials will include the following:

- This protocol
- Investigator brochure
- Manuals of operation (MOO)
- Clinical lab and Bioanalytical lab manuals
- Template source documents
- Informed consent forms
- PRO questionnaires if applicable
- Instructions for randomizing the study drug
- Randomization lists
- Regulatory binder and its contents
- Other study-essential documents

1.17.2 Modifications/Amendments to the Protocol

Protocol amendments will be submitted by sponsor to FDA according to IND Application Reporting requirements, and by sponsor or investigator to IRB according to applicable IRB requirements.

1.17.3 Publication Plan

No publication or disclosure of the study results is permitted, in whole or in part, except to the extent allowed in a separate written agreement, such as the applicable Clinical Trial Agreement between the investigator and the sponsor.

1.17.4 Clinical Study Report

A clinical study report (CSR) following FDA or ICH guidelines, will be prepared and submitted in accordance with local regulations.

1.17.5 Subject Privacy; Authorization to Use and Disclose PHI

The investigator will attempt to assure that subjects' confidentiality is maintained within the limits of the law. All CRFs, CSR, lab reports, study documents, and communications relating to the study, shall not ordinarily identify subjects by their full first and/or last name, but rather be limited to subject ID, initials, and date of birth.

As required by federal regulations, the investigator will allow the sponsor and/or its representatives, access to all pertinent medical records and source documents, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation for inspection.

For the proper conduct of the study and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and local privacy regulations, subjects enrolled in the study will need to provide continuous authorization to allow disclosure and use of their protected health information (PHI). This authorization to use and disclose PHI may be given as part of a separate document or as part of the informed consent form, and must clearly specify which parties will have access to a subject's PHI, for what purpose and for how long.

1.17.6 **Monitoring and Access to Medical Records**

Study progress will be monitored by the sponsor or its representative (eg: a contract research organization) as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and to determine that the study is being conducted in compliance with accepted regulatory requirements. Arrangements for monitoring visits at each site shall be made with reasonable advance notice, except in case of emergency.

During a monitoring visit, the investigator or study team must make office and/or hospital records of study subjects fully available for inspection, verification and copying by the sponsor or its representative.

If the sponsor or its representative is exposed to a subject's medical records or information, the sponsor will comply with all applicable laws and institutional policies regarding the confidentiality and privacy of such records and information, including but not limited to the HIPAA.

1.17.7 **Source Documents**

1.17.7.1 Definition

Source documents include all information, **original** records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents must be:

- **Attributable**: it should be clear who completed the source document
- **Contemporaneous**: the source data should be documented in "real time," as it is acquired. Acceptable amount of delay should be defined and justified
- **Accurate**: data should be a real representation of facts
- **Original, legible, enduring, complete, consistent, credible**, and if possible, **corroborated** (backed up by evidence)

Copies, **scans or transcriptions,** if certified after verification as being accurate and complete can also be considered source.

Adequate records of such source data will be maintained for the study. All original source documentation will remain at each investigator's site. Source data are stored by the investigator in any electronic medical records system typically used at the study site, including measurements that are obtained electronically, which will be printed and retained in the study files.

For more information on "good documentation practice in clinical research," please refer to [102].

1.17.7.2 Examples of source documents

The following original documents, data and records shall be considered source documents: signed informed consents, signed lab reports, signed ECG traces, digital retinal imaging saved on the original hard drive, digital microperimetry data saved on the computer used to acquire microperimetry, medical notes on ocular exam, progress notes and records stored on paper or electronically on site's electronic medical record system, receipt log of drug supply, protocol deviations, work sheets, nursing notes, adverse events reports, check-up phone call logs, information regarding withdrawal, reasons for discontinuation, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the clinical laboratories, and at any reading center involved in the trial.

1.17.7.3 Source document templates provided by sponsor

For each visit, the sponsor may provide template source documents to facilitate the flow of procedures and the collection of data. These source document templates can be used as primary source documents to standardize the format across all sites and facilitate transcription of source data into online case report forms (CRF).

These templates are only for guidance and should not preempt the investigator from inserting any additional source document as required for the performance of the trial. If there are any discrepancies between the template and the protocol, the protocol shall govern.

If a procedure was not performed or the question was not asked or answered, use "Not Done" or "Not answered" as appropriate. If the item is not applicable to the individual case, write "Not Applicable." All entries should be printed legibly, preferably in black ink. If any entry error has been made, to correct such error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **DO NOT ERASE OR WHITE OUT ERRORS**. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

1.17.8 **Case Report Forms**

CRF will be designed in a user-friendly format to facilitate transcription and minimize risks of errors. All data requested on the CRF must be recorded. All missing data must be explained. Electronic CRF forms (eCRF) will be used in this study and stored on a server compliant with FDA regulations on electronic data.

1.17.9 **Case Report Form Completion, Data Storage and Transmission**

After each visit or new data have been collected for a specific subject, study team shall record clinical data required by sponsor into eCRF. . Sponsor or representative may assist sites with inputting trial data in the CRF.

If required by sponsor, a scan of certain source documents, shall be uploaded on the EDC to facilitate monitoring.

Transmission of data into the EDC should preferably be completed within 5 business days of visit or data collection. It is the PI's responsibility to ensure accuracy, completeness, clarity, and timeliness of data reported in the EDC. Unexplained missing data may result in electronic queries by study monitor(s) or sponsor.

The EDC application is password protected and contains an audit trail that records users and the date and time of initial inputs and of any correction.

Once data have been source-data verified (SDV), PI must sign off on the data by providing formal approval of all the information contained in the CRF.

At the end of the study, CRF data and corresponding audit trails will be retained by the sponsor. A copy of the final archival CRF in the form of a compact disk (CD) or other electronic or paper media may be provided to the site and placed in the regulatory binder.

1.17.10 Record Retention

The investigator is responsible for retaining study essential documents, sources and CRFs according to the clinical trial agreement, GCP and ICH E6(R)2 guidance, which may be amended from time to time. Sponsor should inform the investigator/institution as to when these documents no longer need to be retained.

Should PI withdraw their responsibility to maintain the study records, they must place study records in safekeeping, and inform sponsor of records location and of the contact information for the person/entity assuming responsibility for them. Sponsor may also store records on behalf of PI.

1.17.11 Protocol Deviation

Investigator *shall not deviate from the protocol*.

Nonetheless, *protocol deviations or changes intended to eliminate an apparent immediate hazard* to human subjects may be implemented immediately, provided that sponsor and IRB are subsequently notified. Such notice shall be given no later than 5 working days after the emergency occurred, or sooner as applicable by law or local regulations.

In addition, *planned deviations may be approved* by sponsor, and by IRB when necessary. In certain cases, FDA review may be required, in which case such planned deviations may be implemented only after receiving confirmation by sponsor that the FDA review period has been completed. Sponsor will be responsible for submitting all requests and protocol amendments to the FDA and other applicable regulatory agencies.

Each and every protocol deviation should be documented.

1.17.12 Approval Exceptions and Items and Services Requiring Sponsor Approval

Approvable exceptions may be granted by sponsor to the extent allowed in specific sections of this protocol, or for *items and services requiring sponsor approval*.

Such approval should only be granted if it is believed not to be of clinical or scientific significance and would not be expected to have significant effect on the results of the study. The approval should be documented.

1.17.13 Site or Trial Termination

For reasonable cause, the investigator, IRB, SMC, or sponsor, may terminate the study at a given site or at all sites. Conditions that may warrant termination include but are not limited to:

- Investigator non-compliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Delayed or poor communication between the sponsor and the investigator
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by FDA or other regulatory authority

Written notification that includes the reason for protocol or site termination is required.

1.17.14 **End of Trial**

For regulatory purposes, the "end of the trial" is defined as database lock, unless a different time is announced by sponsor.

1.17.15 **Ownership/Confidentiality of study data and documents**

Any and all scientific, commercial and technical information disclosed by sponsor to investigator is considered confidential and proprietary property of sponsor, and is bound by the agreements between the sponsor, the site, the investigator and the study team.

The investigator understands that information developed from this clinical study will be used by sponsor in connection with the development of the study drug, and therefore may be disclosed by sponsor to other clinical investigators, the FDA, or to other government agencies. The investigator also understands that, in order to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide the sponsor with *complete test results and all data* developed during the performance of this study.

1.18 STUDY MONITORING, AUDITING, AND INSPECTING

1.18.1 **Monitoring Plan**

The sponsor will perform on-site monitoring visits as frequently as necessary, following a risk-based approach, and as detailed in a monitoring plan. A draft monitoring plan is found in section 1.22.4.

Monitoring shall be performed to ensure adherence to good clinical practices and the protocol, and to ensure quality of the collected data.

Monitor will record dates of visits in a study site visit log kept at the site. At each visit, monitor will attempt to review study documents, including regulatory binder, source documents, patient records and study-essential documents.

Source documents, their nature and location will be identified to ensure that monitor is aware of source documents and has access to them for verification. Investigator will allocate sufficient time for and be accessible during such monitoring activities, and will ensure that the monitor has suitable space and time to conduct the monitoring visit.

After the monitoring visit, monitor will send a report to investigator with their findings.

1.18.2 **Auditing and Inspecting**

Investigators will permit study-related audits and inspections by sponsor or authorized auditors, IRB, or government regulatory bodies, of all study-related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). Investigators will guarantee direct access to these documents and support at all times for these activities. Medical records and other study documents may be copied during the audit or inspection, provided that subject names and other private information are masked to preserve confidentiality.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities. The investigator should immediately notify sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection, and sponsor should be allowed to be present during such inspection.

1.19 ETHICAL CONSIDERATIONS

1.19.1 GCP conduct of the Trial

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

1.19.2 Institutional Review Board

This protocol and any amendments will be submitted by the sponsor or by each site's study team, to a properly constituted Institutional Review Board (IRB) for formal approval of the study conduct at the site. Each IRB should be in compliance with the general standards for composition, operation, and responsibility of an IRB set forth in ICH guidelines for GCP Sections 3.1 to 3.4 and 21 CFR part 56. A central IRB can be used.

The investigator in collaboration with sponsor or representative, shall be responsible for reporting to the IRB all changes in research activity, including protocol amendments, updates of Investigator's Brochures, investigational new drug (IND) safety reports, all unanticipated problems involving risks to human subjects, study termination, and other reporting required by the IRB . The investigator will also be responsible for submitting progress reports and annual renewal reports to the IRB at regular intervals appropriate to the degree of subject risk involved, but no less than once per year.

Copies of all IRB notifications and approvals, including approved informed consent forms, shall be included in the regulatory binder and provided to the sponsor. The investigator should also provide a current list of all IRB members after all submissions.

1.19.3 Subject Information, Informed Consent

General information: Informed consent must be obtained from each subject before starting to perform any protocol-related activity. The informed consent form (ICF) shall first be approved by the sponsor prior to its submission to the IRB. The ICF will comply with all applicable regulations governing the protection of human subjects.

Only the investigator, or appropriately-trained designee shall be authorized to obtain informed consent. The name of any investigator-appointed designee should be provided to the sponsor in a delegation log, and appropriate training documentation kept in file.

Informed consent process*:* All prospective study subjects will be provided the IRB and sponsor-approved ICF describing this study and providing sufficient information to make an informed decision about participation in this study. The investigator or authorized designee must explain the nature of the study and the treatment in such a manner that the subject is aware of his/her rights and responsibilities, as well as potential benefits and risks. The study team shall also answer any questions that might arise throughout the study and share any new information, in a timely manner, that may be relevant to the subject's willingness to continue his/her participation in the trial.

Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without their decision influencing their current or future care. Sufficient time should be given for prospective subjects to review the ICF and ask questions. Once all of their questions have been answered and they have voluntarily agreed to participate in the study, subjects will be asked to sign and date the ICF. Documentation of the discussion and the date of informed consent must be recorded in the

subject's medical record or a study/clinic chart. Subjects who cannot give informed consent (i.e., mentally incompetent patients or those physically incapacitated) are not to be recruited into the study. Subjects who are competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian.

A printed copy of all signed informed consent documents must be given to the subject.

1.20 STUDY FINANCES

1.20.1 **Funding Source**

This study will be funded by the sponsor.

1.20.2 **Financial Disclosure / Conflict of Interest (21 CFR 54.4)**

The study is a "covered clinical study". For compliance with regulations, the following study team members will be required to fill out a "financial disclosure form":

- PI,
- Other members of the study team, if they are directly involved in the treatment or evaluation of study subjects,

The form shall be updated if any relevant changes occur during the study and for one year following the study completion or the end of the study team member's participation.

Note that staff members who provide ancillary or intermittent care, or those providing routine tests (such as vital signs, ECG, etc.) do not need to fill out the financial disclosure form.

1.20.3 **Subject Stipends or Payments**

Upon IRB approval, subjects may be given gift cards to defray travel, hotel or other expenses associated with each visit. Each site's informed consent form will provide specific details and gift card amounts, which must be IRB approved.

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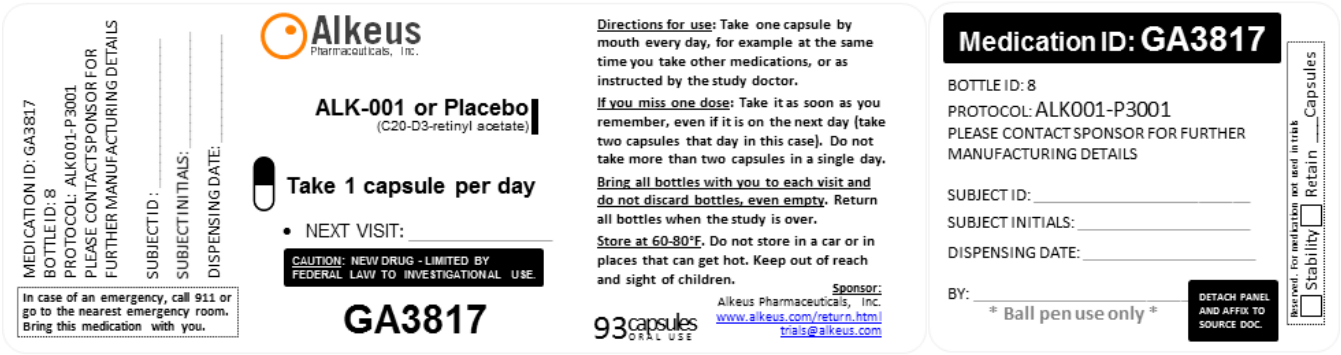
1.22 ATTACHMENTS

- Sample Investigational Drug Label
- Visual Function Questionnaire-25 (VFQ-25)
- Functional Reading Independence (FRI)
- Draft Monitoring Plan

1.22.1 **Sample Investigational Drug Label**

("**GA3817**" is an example of a random medication ID number, shown here only as an example). The label has a matte finish and **only ball pen** should be used to write on it (other types of ink will smudge or fade).



1.22.2 **Visual Function Questionnaire - 25**

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

(Circle One)

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. **How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:**

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. **Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?**

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. **How much difficulty do you have reading street signs or the names of stores?**

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

16. How much difficulty do you have <u>driving at night</u>? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16A. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me..	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not	

interested in doing this 6

SUBSCALE: DRIVING

A10. [This item, "driving in difficult conditions", has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight	1	2	3	4	5

1.22.3 Functional Reading Independence Index (FRI)

The Functional Reading Independence Index (FRI Index)

Please read the following instructions to the patient.

Instructions to Patient:

We are interested in learning more about how your vision affects your everyday reading. I'm going to ask you about seven (7) activities that involve reading. If you wear eyeglasses or contact lenses, please answer all the questions as if you were wearing them during the activity.

Please take as much time as you need to answer each question. Remember, there are no right or wrong answers. All of your answers are confidential. Do you have any questions before we begin?

Please think about your vision over the past 7 DAYS when answering each question.

1. In the past 7 DAYS, did you read written print such as books, magazines or newspapers?	☐ Yes ☐ No
If "Yes"	**I'd like to know more about that. I will read you a list of statements – Please answer "Yes" or "No" to each:** a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the text closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? *(example, if needed:* using a large print book) ☐ Yes ☐ No e. Did another person help you read written print such as books, magazines or newspapers? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 2.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? Please choose one answer. *(Go to Question 2)*
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? Please choose one answer. *(example, if needed:* no time or opportunity to read written print*)*

2. In the past 7 DAYS, did you read to pay bills or write a check?		☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each:	
	a. Did you use extra lighting?	☐ Yes ☐ No
	b. Did you move the bill or text closer to you?	☐ Yes ☐ No
	c. Did you use a magnifying glass?	☐ Yes ☐ No
	d. Did you use any other vision aids, not already mentioned? *(example, if needed:* using a check-writing template*)*	☐ Yes ☐ No
	e. Did another person help you read to pay bills or write a check?	☐ Yes ☐ No
	↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 3.*	
	f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 3)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to pay bills*)*	

3. In the past 7 DAYS, did you read in order to take your medicine such as reading a prescription, medicine label, or a syringe?		☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each:	
	a. Did you use extra lighting?	☐ Yes ☐ No
	b. Did you move the medicine bottle or prescription closer to you?	☐ Yes ☐ No
	c. Did you use a magnifying glass?	☐ Yes ☐ No
	d. Did you use any other vision aids, not already mentioned?	☐ Yes ☐ No
	e. Did another person help you read in order to take your medicine?	☐ Yes ☐ No
	↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 4.*	
	f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 4)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need to take medicines*)*	

4.	**In the past 7 DAYS, did you read labels such as price tags, food labels, or clothing labels?**	☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the price tag or label closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read labels? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 5.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 5)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to read labels*)*	

5. In the past 7 DAYS, did you make or receive a telephone call that required you to read the numbers on a telephone, answering machine or caller-ID device? This includes cell phones.	☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting or less lighting? ☐ Yes ☐ No b. Did you move the telephone closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No *(example, if needed: using a "talking caller-ID")* e. Did another person help you read to make or receive a telephone call? ☐ Yes ☐ No ↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 6.* f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 6)*
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to make phone calls*)*

6.	**In the past 7 DAYS, did you read words or numbers on your screen while watching television?**	☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each:	
	a. Did you use less lighting?	☐ Yes ☐ No
	b. Did you move closer to the television?	☐ Yes ☐ No
	c. Did you use a magnifying glass?	☐ Yes ☐ No
	d. Did you use any other vision aids, not already mentioned?	☐ Yes ☐ No
	e. Did another person help you read words or numbers on the television screen?	☐ Yes ☐ No
	↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to Question 7.*	
	f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to Question 7)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to watch television*)*	

7. In the past 7 DAYS, did you read when using a computer?		☐ Yes ☐ No
If "Yes"	*If needed:* I will read you a list of statements – Please answer "Yes" or "No" to each:	
	a. Did you use less lighting or change the contrast on the screen?	☐ Yes ☐ No
	b. Did you move closer to the computer screen or increase the font size?	☐ Yes ☐ No
	c. Did you use a magnifying glass?	☐ Yes ☐ No
	d. Did you use any other vision aids, not already mentioned?	☐ Yes ☐ No
	e. Did another person help you read when using a computer?	☐ Yes ☐ No
	↓ *If "Yes" to Item e, ask Item f.* *If "No" to Item e, go to concluding statements.*	
	f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? *(Go to concluding statements)*	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? *(example, if needed:* no need or opportunity to use a computer*)*	

This concludes our interview. Thank you for your time.

1.22.4 **Clinical Trial Monitoring Plan (Draft)**

Clinical Trial Monitoring Plan (CTMP)

Alkeus Pharmaceuticals, Inc.

Draft

April 2018

This plan will be implemented to monitor the clinical sites approved for performance of this protocol under an Investigational New Drug (IND) application. Standard Operating Procedures for Monitoring Clinical Trials established by each study site of study, if existing, will complement the monitoring activities.
Monitoring will be performed by the sponsor or an alternative qualified Monitor.

Purpose of Monitoring Plan

The purpose of this monitoring plan is to present a potential approach to monitor the present clinical study. The plan complies with good clinical practice (GCP) guidelines (5.18.1), FDA guidelines and FDA regulations (21 CFR 312 and 812), which require monitors to verify that:

(a) the rights and well-being of human subjects are adequately protected.

(b) the reported trial data are accurate, complete, and identical to the source documents.

(c) the conduct of the trial is in compliance with the approved protocol, with GCP, and with applicable regulatory requirements.

This document identifies key monitoring activities and specifies the data to be reviewed over the course of the clinical trial. The monitor will conduct visits in accordance with this plan.

Scope of Monitoring

In compliance with GCP guidelines, monitors will verify that data collected on data collection forms (CRFs) match the source documents. Source documents are defined as any original records or data related to the trial or to subject treatment or medical history. Source documents include: original hospital, clinical, and office charts, laboratory notes, subject diaries or evaluation checklists, pharmacy records, recorded data from automated instruments, transcriptions (certified to be accurate after verification), magnetic media, or x-rays. *(GCP 1.5.2*)

The monitor will compare the practices and procedures of the investigator with the commitments made in the protocol and regulatory applications (e.g. IND, IRB). *(FDA Compliance Program Guidelines, Part III)*

The monitor's primary responsibilities (GCP 5.18.4) when relevant to the clinical trial are to:

3.1 Verify the investigator's adequate qualifications to safely and properly conduct the trial. To accomplish this, the monitor will:

- Review the study regulatory file to verify there is a CV or other documentation of qualification for each investigator.
- Verify that each CV was current at the time of study initiation.

3.2 Verify that facilities, including laboratories and equipment, remain adequate throughout the trial. To accomplish this, the monitor will:

- Verify that the regulatory file contains current certifications and lab normal ranges for the laboratory performing protocol-required procedures or tests.

3.3 Verify storage, dispensing, instructions for use, and disposition of the investigational product complies with regulatory requirements.

DRUGS

The monitor will check the product disposition records, protocol, regulatory file, or subject files to:

- Assess whether the site stores the product under the conditions specified in product labeling or packaging.
- Verify that the protocol or the regulatory file documents how subjects are provided with necessary instruction on how to use, handle, store, and return product.
- Verify that the time the product has been stored does not exceed the shelf life specified in the labeling or packaging.
- Verify the site has documentation in the regulatory file of receipt of disposition/use and return of product.
- Verify the regulatory file contains manufacturer guidelines or other instructions for handling product.
- Verify the site maintains records that indicate product has been supplied only to eligible subjects at protocol specified doses.

3.4 **Verify that the site follows the approved protocol.** To accomplish this, the monitor will:

- Verify the (current) IRB approved protocol and the (current) protocol in the regulatory file are the same.
- Compare data to be collected on case report forms (CRFs) with the IRB approved protocol (data collection should not exceed the limits defined by the protocol).
- Verify that the number and type of subjects entered into the study was confined to the number and type the protocol defined eligible.
- Verify that no deviations from or changes to the protocol have been implemented without prior review and documented approval of the IRB (except where necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.)
- Verify the labels on the individual patient bottles/medical devices comply with the requirements for investigational drug or device labeling.

3.5 **Verify that written consent was obtained before subjects' participation**. To accomplish this, the monitor will:

- Verify that correct version of IRB-approved consent form was used.
- Verify the date the consent form was signed and dated.
- Verify, against the subject's medical record, source documentation that the consent was signed before any research test or procedure was performed.
- Verify that the subject signed and dated a HIPAA form prior to enrollment, as applicable.

3.6 **Ensure trial staff is adequately informed about the trial and has not delegated responsibilities to unauthorized individuals**. To verify this, the monitor will:

- Note the identity of all persons and locations involved in the collection of data by looking at the Delegation of Responsibility Log. (FDA Compliance Program Guidelines, Part III) (If there is no site Delegation of Responsibility log, the monitors will require that one be completed and updated throughout the trial).
- Check documentation for information about distribution of the currently approved protocol and Investigator Brochure to the study team.
- Check documentation of any protocol specific training of authorized individuals.
- Compare study documents, the IRB application, and the Delegation of Responsibility log to determine whether responsibilities have been delegated to unauthorized individuals.

3.7 **Verify that only eligible subjects are enrolled**. To accomplish this, the monitor will:

- Verify whether the existence of the condition for which the investigational product is being studied is documented by a compatible history.
- Determine, when possible, whether the existence of the condition is documented by notation made prior to the initiation of the study.
- Compare the protocol inclusion/exclusion criteria against the subject's medical record, or other source documentation, to determine whether the enrolled subject is eligible for inclusion in the study.

3.8 **Report subject recruiting and enrollment rate**. To accomplish this, the monitor will:

- Count the number of subjects enrolled (defined by this plan as having signed a consent form) and compare this number to the limit approved by the IRB. (FDA Compliance Program Guidelines, Part III)
- Check subject screening/enrollment log to document subjects who entered pretrial screening but did not give consent to participate. (The enrollment log may be incorporated within the screening log.)

3.9 **Verify trial records are accurate, complete, and current**. To accomplish this, the monitor will:

- Verify that the investigator or assigned designee has completed current CRFs – and that they are signed and dated appropriately.
- Verify that source documentation was used to complete CRFs.
- Verify that the protocol identifies source data that will be recorded directly on CRFs (with no prior written or electronic record of data).
- Verify whether clinical laboratory testing (including EKGs, X-rays, eye exams, etc.), as noted in the case report forms, is documented by the presence of completed records among the source documents. (FDA Compliance Program Guidelines, Part III)
- Verify the site's data and source documents in terms of their organization, condition, completeness, and legibility. (FDA Compliance Program Guidelines, Part III)
- Verify the investigator has made required reports and submissions to the IRB, Sponsor and, if applicable, the FDA.
- Verify the information in the reports to information in the Regulatory file and source

documents to verify accuracy and completeness, including reports of any adverse experiences.

3.10 **Check the accuracy and completeness of CRF entries, source documents, and other trial-related records against each other**. To accomplish this, the monitor will:

- Verify the data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents.
- Verify any dose or therapy modifications are well documented.
- Verify adverse events, concomitant medications, and underlying illnesses are reported accurately on the CRFs, in accordance with the protocol.
- Verify CRFs reflect all visits that subjects fail to make and all tests or examinations that are not performed.
- Verify subject deaths, withdrawals, dropouts, and subjects lost to follow-up are reported and explained on CRFs.
- Verify, by looking at the CRF in the subject binder/folder, that all applicable forms are completely filled out if any subject has withdrawn or dropped out of the study since enrollment and that an explanation is provided.

3.11 **Inform the investigator of any CRF errors and ensuring appropriate corrections are made, dated, explained (if necessary), and initialed by the investigator or designee**. To accomplish this, the monitor will

- Inform the investigator of any CRF entry error, omission, or illegibility.
- Ensure that appropriate corrections, additions or deletions are made, dated, explained (if necessary), and initialed by the investigator or his/her designee authorized to make such changes. (This authorization must be documented on the site responsibility log).

3.12 **Determine whether all adverse events are reported appropriately**. To accomplish this, the monitor will:

- Verify that serious adverse events have been reported to the IRB, and, if applicable, Sponsor by looking at correspondence files and comparing against subject medical records. (FDA Compliance Program Guidelines, Part III)
- Verify, by reviewing correspondence files and comparing against subject medical records, that the reporting to the IRB of Unanticipated Problems has been followed according to the site specific IRB's rules:
    - Any serious event (including on-site and off-site adverse events, injuries, side effects, deaths or other problems) which, in the opinion of the local investigator, was unanticipated, involved risk to subjects or others, and was at least possibly related to the research procedures;
    - Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur;

- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
- Any publication in the literature, safety monitoring report (including Data and Safety Monitoring Reports), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
- Any breach in confidentiality that may involve risk to the subjects or others;
- Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the study team; or
- Any other serious and possibly related event which, in the opinion of the investigator, constitutes an unanticipated risk.

- Verify, by looking at subject medical records, that events not meeting the reporting requirement are nonetheless captured on the IRB continuing review report.
- Verify that all adverse events that are required by FDA regulation to be reported to the FDA have been reported within the specified time frames.

3.13 **Determine all essential documents are maintained**. To verify this, the monitor will:

Verify that all applicable documents exist and are current as of date of monitoring. The following documents, if applicable, are essential documents:

- Transfer of Monitoring Obligation Agreement
- IRB, FDA, and other regulatory documents (e.g. reports, correspondence)
- Signed protocol
- Investigator brochure
- Consent form and IRB-approved information for subjects
- Randomization procedure
- Sample CRF or document stating medical record is data collection form
- Investigator and sub-investigators CV or documentation of qualifications & training
- Site signature log / Delegation of Responsibility Log
- Lab normal ranges
- Lab certifications
- Screening log
- Enrollment log
- Adverse event log
- Correspondence
- Subject code list
- Product accountability log
- Product handling and storage instructions
- Product shipping records and certificates of analysis
- Record of retained samples
- Decoding procedures for masked trials
- Record retention plan

- Monitoring reports

3.14 **Obtain copies of all study-related correspondence with the FDA, when needed**.

3.15 **Communicate deviations from the protocol, GCPs, or regulatory requirements to the investigator and taking appropriate action to prevent recurrence of the deviations.** To accomplish this, the monitor will:

- Verify subject visits have taken place as stated in protocol by checking the subject tracking log.
- Verify all tests have been completed as stated in the protocol by looking at source documentation and CRFs.
- Verify any noncompliance issues with protocol (subject) by looking at CRFs and other source documentation.
- Verify if any visit was out of allowable time deviation by looking at subject visit schedule.
- Verify any other deviations by comparing the protocol with source documentation and/or subject CRFs.

Extent of Data Monitoring
Monitors will review clinical data that affect study endpoints defined in the protocol. Data collected for reasons other than to support protocol-defined endpoints will not be monitored.

The extent of subject data monitoring will include verifying:

- Initial study consent : 100% of enrolled subjects;
- Study eligibility : 100% of enrolled subjects;
- Data to support protocol defined endpoints : 100% of completed subjects

In addition to monitoring subject data, the monitor will review the regulatory file for any additions to GCP-required documents since the last visit. Monitors will, at their first and last monitoring visits, review the regulatory file for the presence, completeness, and accuracy of all GCP-required documents.

Transfer of Monitoring Obligation Agreement
A signed Transfer of Monitoring Obligation Agreement will be obtained from all sponsors and principal investigators, if applicable.

Site Visit Confirmation
After scheduling a monitoring visit with the site the following will occur:

- The monitor will review previous monitoring reports to identify any unresolved issues.

Debriefing the Investigator
At the end of each monitoring visit, the monitor will meet with the investigator or coordinator to go over any findings of the visit.

Documentation of Findings
The monitor will send a monitoring report to the study sponsor and to the study investigator. A copy of every monitoring report will be retained by the sponsor and the monitor.

The monitoring report will describe the progress of the study, the findings of the visits, unresolved issues, and follow-up required. The monitor will keep an electronic copy of the report and a signed copy will be maintained in the Regulatory file. Follow-up items will be checked and documented at the next monitoring visit. The report will include, but will not be limited to, the following:

- A list of records reviewed, i.e. subject charts, hospital records, lab slips, etc.;
- Number of case report forms reviewed by research subject number and visit date;
- Statement that test article accountability records were or were not sufficient;
- Statement regarding whether there was any evidence of under-reporting of adverse events;
- Statement regarding protocol adherence

(FDA Compliance Program Guidelines, Part III)

Frequency of Visits
The monitor will provide monitoring before, during, and at the end of clinical trials.

In general, monitoring visits should be scheduled according to a "risk-based monitoring" approach as found in FDA guidance (August 2013).

The following schedule can be used as a suggestion:

- *Site Initiation Visit (SIV):* After IRB approval but prior to enrolling the first subject;
- *First monitoring visit*: As soon as possible after the first subject is enrolled;
- *Risk-based interim monitoring visits (IMV):* as needed based on risk, or about 3 weeks after first subject is enrolled;
- *Close-out visit (COV):* After the last subject has completed his/her participation in the study.

This monitoring schedule may be revised based on the following considerations:

- Accrual rate
- History of protocol deviations or non-compliance with GCPs
- Number of data corrections required
- Study stage (e.g. start-up or follow-up)
- Complexity of the trial
- IRB request

Interface with the Office of Regulatory Affairs
The monitor will report the following situations, should they occur, to the Office of Research Compliance and Regulatory Affairs:

- Persistent failure by the sponsor, investigator, or other member of the study team to follow the protocol;
- Persistent failure by the sponsor, investigator, or other member of the study team to follow GCP guidelines;